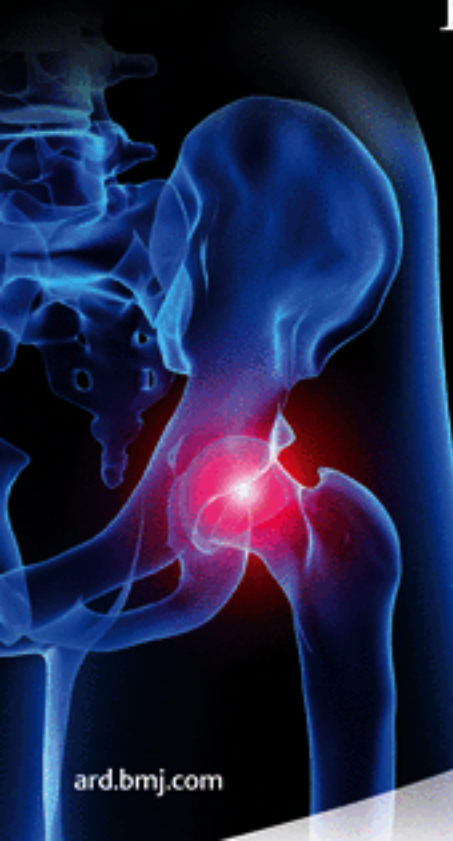
February 2018 Volume 77 Issue 2

Impact Factor 12.811

Annals of the Rheumatic Diseases

The EULAR Journal



ard.bmj.com

eular BMJ

ARD
The EULAR Journal

Guidelines for Authors and Reviewers

Full instructions are available online at http://ard.bmj.com/pages/authors. Articles must be submitted electronically at http://mc.manuscriptcentral.com/ard. Authors retain copyright but are required to grant ARD an exclusive licence to publish. (http://authors.bmj.com/submitting-your-paper/copyright-and-authors-rights).

Annals of the Rheumatic Diseases publishes original work on all aspects of rheumatology and disorders of connective tissue. Laboratory and clinical studies are equally welcome

Subscription Information

ARD is published monthly; subscribers receive all supplements
ISSN 0003-4967 (print); 1468-2060 (online)

Institutional Rates 2018

Print
£986

Online
Site licences are priced on FTE basis and allow access by the whole institution. Details available online at http://journals.bmj.com/content/subscribers or contact the Subscription Manager in the UK (see above right)

Personal Rates 2018

Print (includes online access at no additional cost)
£407

Online only
£173

Eular congress delegates
Delegates receive a Continuous Professional Development package that includes a 12 month complimentary subscription to *ARD* in print and/or online

Personal print or online only and institutional print subscriptions may be purchased online at http://journals.bmj.com/content/subscribers (payment by Visa/Mastercard only)

Residents of some EC countries must pay VAT; for details, call us or visit http://journals.bmj.com/content/subscribers

Contact Details

Editorial Office
Annals of the Rheumatic Diseases
BMJ Publishing Group Ltd
BMA House
Tavistock Square
London WCIH 9JR,UK
T: **+44 (0)20 7383 6250**
E: **ard@bmj.com**

Permissions
http://www.bmj.com/company/products-services/rights-and-licensing/permissions

Supplement Enquiries
T: **+44 (0)20 7383 6057**
E: **journals@bmj.com**

Subscriptions
For all subscription enquiries and orders
T: **+44 (0)20 7111 1105**
E: **http://ard.bmj.com/pages/subscribe**

Display Advertising Sales
Sophie Fitzsimmons
T: **+44 (0)20 7383 6783**
E: **sfitzsimmons@bmj.com**
http://www.bmj.com/company/raise-visibility-and-reach

Online Advertising Sales
Marc Clifford
T: **+44 (0) 20 7383 6161**
E: **mclifford@bmj.com**
http://www.bmj.com/company/raise-visibility-and-reach

Display & Online Advertising Sales (USA)
American Medical Communications (AMC)
T: **+1 973 214 4374**
E: **rgordon@americanmedicalcomm.com**

Author Reprints
Reprints Administrator
E: **admin.reprints@bmj.com**

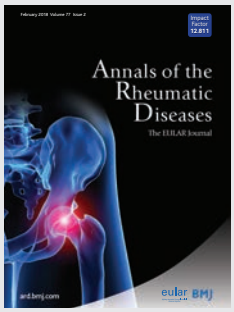
Commercial Reprints (except USA & Canada)
Nadia Gurney-Randall
T: **+44 (0)20 8445 5825**
M: **+44 07866 262344**
E: **ngurneyrandall@bmj.com**

Commercial Reprints (USA & Canada)
Ray Thibodeau
T: **+1 267 895 1758**
M: **+1 215 933 8484**
E: **ray.thibodeau@contentednet.com**

EULAR
Eular Executive Secretariat
Seestrasse 240, 8802 Kilchberg, Switzerland
E: **eular@eular.org**
www.eular.org

For all other ARD contacts
http://ard.bmj.com/contact-us

ARD
The Eular Journal



Editorial office
Annals of the Rheumatic Diseases
BMJ Publishing Group Ltd
BMA House
Tavistock Square
London WCIH 9JR,UK
T: **+44 (0)20 7383 6250**
F: **+44 (0)20 7383 6668**
E: **ard@bmj.com**
Twitter: **@ARD_BMJ**
ISSN: 0003-4967 (print)
ISSN: 1468-2060 (online)
Impact Factor: 12.811

ARD is published by BMJ Publishing Group Ltd typeset by Exeter Premedia Services Private Ltd, Chennai, India and printed in the UK on acid-free paper.

Annals of the Rheumatic Diseases (ISSN No: 0003-4967) is published monthly by BMJ Publishing Group and distributed in the USA by Air Business Ltd. Periodicals postage paid at Jamaica NY 11431 POSTMASTER: send address changes to *Annals of the Rheumatic Diseases*, Air Business Ltd, c/o Worldnet Shipping Inc., 156-15, 146th Avenue, 2nd Floor, Jamaica, NY 11434, USA.

MORE CONTENTS ▶

Basic and translational research

Letters

Electronic pages

Correspondence

Bout of the corner men and not the boxers? Contextual effects flex their muscles

Martin Englund[1,2]

Increased use of MRI in the quest to explain symptoms, and patients' hope for a 'quick-fix', often challenge healthcare professionals in their choice of treatment for the painful ageing knee. In the USA, there are about one million knee arthroscopies per year and the majority involve removal of torn meniscal tissue in middle-aged patients. The absolute number of arthroscopic partial meniscectomies (APMs) in Europe is unknown but may be even greater due to the larger European population. The popularity of this procedure is understandable — multiple case series and randomised controlled trials (RCTs), not to mention doctors' personal observations of patients, show sustained improvement after APM. However, the last few years, the efficacy of the *actual therapeutic element*, resection of meniscal tissue, has been called into question.

A hallmark RCT is the exquisitely designed, randomised, double-blinded, sham-surgery-controlled Finnish Degenerative Meniscal Lesion Study (FIDELITY).[1] The main findings of the trial so far are summarised in these short film clips:

- FIDELITY New Engl J Med 2013
- FIDELITY Ann Intern Med 2016

In the provocative *New Engl J Med* article from 2013, Sihvonen *et al* reported that outcomes in the middle-aged patients, where resection of meniscus was only simulated during the diagnostic arthroscopy, were very similar to those of actual APM. Patients in *both* the APM arm and the sham-surgery arm improved substantially and sustainably, indicating that the improvement observed after APM is attributable to what are collectively referred to as *contextual effects*. Thus, it was *not* the actual therapeutic element of the surgery, which is resection of torn meniscal tissue. Now, in the present 2-year follow-up of the FIDELITY patients,[2] Sihvonen *et al* strengthen their original findings. The investigators report that the lack of treatment effect of APM compared with sham surgery is sustained even at longer follow-up. Further, they found no support that patients with the so-called 'mechanical symptoms' or certain meniscal tear characteristics would have larger improvement.

Contextual effects in chronic pain conditions predominantly include *placebo response* and the *regression to the mean* phenomenon. Although placebo remains an utterly complex entity that is not fully understood, it is likely to be very powerful in surgical interventions. It fact, it has even been suggested that surgery may offer the 'ultimate placebo'.[3] Additionally, regression to the mean is highly likely to contribute, given that the patient with chronic knee pain often shows a natural history of flares followed by periods of improvement, and that he/she consults and gets included in a trial when he/she is in a bad phase (figure 1). This phenomenon, which substantially may contribute to the total treatment effect, is unknown or forgotten by many researchers and clinicians (and unknown to most medical writers and patients), who often tend to attribute improvement solely to the treatment provided.

The lack of treatment effect of removal of torn meniscal tissue per se in the painful ageing knee may be explained by the misguided reason for which the surgery is often performed. Meniscal lesions confirmed by MRI are typically assumed to explain the patients' knee symptoms. The term 'symptomatic meniscus tear' is heavily misused. Evidence does not support such clear-cut assumption of causality.[4 5] Additionally, as pointed out by Neogi *et al*,[6] a factor can be strongly causally associated with pain in osteoarthritis, yet it may not be a strong predictor of the pain on its own because several other factors may contribute to the pain experience. Thus, deductive reasoning that removal of meniscal tissue somehow would resolve the pain is unfortunately often too simplistic. Naturally, on one end of the spectrum of meniscal tears, there exist cases where a large dislocated longitudinal (bucket-handle) tear of the meniscus (typically a result of major knee trauma) causes painful locking of the knee. Here, arthroscopy is indicated for repair or removal of the torn piece of meniscus. However, there is a grey zone between such an acute *traumatic* meniscal tear and the more slowly developing *degenerative meniscal lesion*.[7] The latter is a frequent incidental finding suggestive of incipient osteoarthritis or simply an ageing joint.[8]

In 2016, the European Society of Sports Traumatology, Knee Surgery and Arthroscopy released new treatment guidelines with the message to refrain from surgery in favour of non-surgical management as the first line of treatment in patients having knee joint symptoms and a degenerative meniscal lesion.[9] Further, most recently, after an extensive meta-analysis, the *BMJ* has also released its clinical guidelines firmly recommending *against* APM in this patient category.[10] Thus, there is

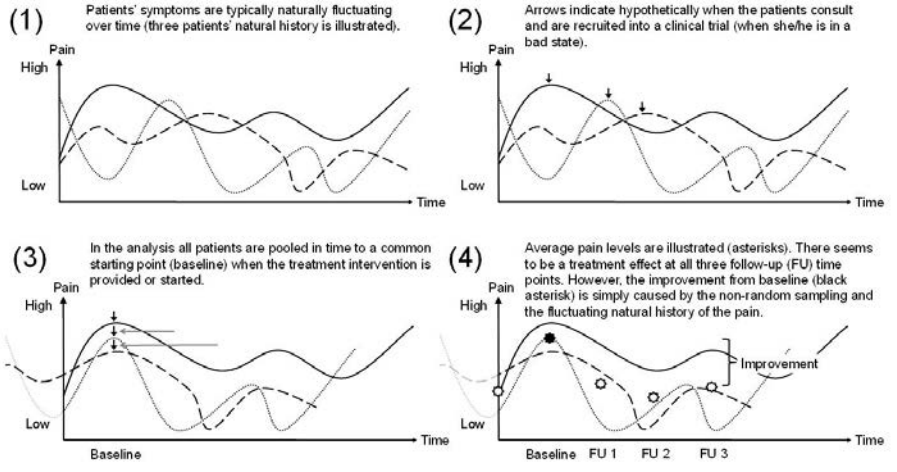


Figure 1 Illustration of regression to the mean.

[1]Department of Clinical Sciences Lund, Clinical Epidemiology Unit, Orthopaedics, Lund University, Lund, Sweden
[2]Clinical Epidemiology Research and Training Unit, Boston University, School of Medicine, Boston, MA, USA

Correspondence to Dr Martin Englund, Clinical Epidemiological Unit, Wigerthuset, Remissgatan 4, Lund University, 221 85 Lund, Sweden; martin.englund@med.lu.se

currently a strong movement for *non-surgical* management of the painful knee — this is typically through a supervised or non-supervised exercise intervention. However, while the effect of APM per se has had its fair share of attention, there is as of yet *no* RCT demonstrating any effect of an exercise intervention above placebo, either for the osteoarthritic knee or for the hip. In contrast, the two RCTs that specifically addressed this topic have *failed* to demonstrate any effect of exercise above a placebo intervention.[11 12] Various claims can be made of the two studies' limitations, but the fact remains (in line with APM) that there is currently *no* evidence that supports a treatment effect on patient-relevant outcomes above placebo, even for exercise therapy. In addition, the concept of strong muscles as preventive of knee osteoarthritis has recently been challenged by observational data.[13] Vested interests, publication bias and wishful thinking may not only exist in the field of orthopaedic surgery.

Interestingly, so far, the *only* clinical trial comparing exercise versus APM *without* added exercise after APM yielded essentially the same outcomes in *both* arms.[14] Now, what does that tell us? If the effect of APM per se is virtually 'nothing', as strongly suggested by the FIDELITY trial (and applauded by the exercise community), is exercise *also* all about placebo and regression to the mean? Or is the placebo response slightly weaker in the exercise intervention arm, supplemented by some true treatment effect? Nota bene, the randomisation is expected to have balanced the two arms with respect to regression to the mean. Thus, that particular component of the total effect is expected to be equal in both treatment arms. Unfortunately, we do *not* yet know how the placebo responses compare between a single arthroscopic intervention and being cared for at regular intervals by a physiotherapist. Still, I think it is fair to conclude that the added *true* component effect attributable to exercise per se seems, at best, to be very modest, if present at all. Thus, it would be intriguing to tease out the true component effect of exercise on the total effect on patient-relevant outcomes. Double-blinded, placebo-intervention trials in this field may be challenging to design and execute but are far from impossible. The challenge is to remove the actual therapeutic element(s) of exercise in the sham arm while keeping the other circumstances of the treatment interventions as identical as possible. In fact, one could consider a trial comparing a very 'low dose' versus 'therapeutic dose' of exercise. 'Too low dose of exercise', after all, is the most commonly heard argument[15] to explain disappointing results such as those from the two placebo-controlled trials already performed.[11 12]

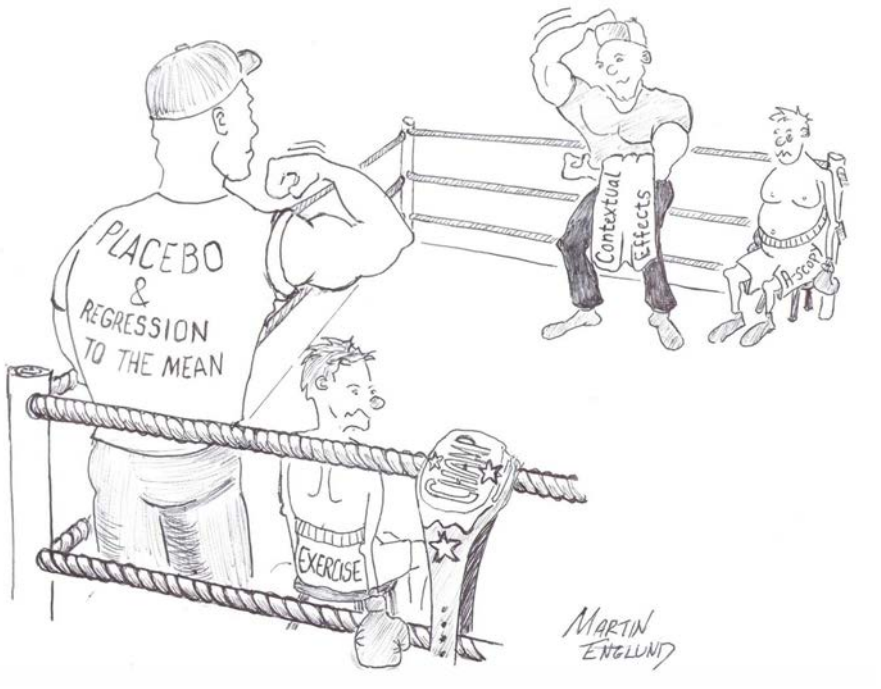


Figure 2 The bout of the corner men and not the boxers?

Nevertheless, a strong, and in my opinion pivoting advantage for an exercise intervention as one of the current primary treatment modalities for the painful ageing knee, is that it is *safe*. Furthermore, increased physical activity, especially if the patient has previously been sedentary, will most likely have a general positive effect on both mental and physical health. Consequently, in a *pragmatic* view, there is in my mind no doubt that exercise should be the treatment offered early on given the current limited availability of other treatment options. Somewhat cynically — and provocatively I might add — to tailor and optimise the most cost-effective, patient-compliant and safe placebo intervention for this massive patient category should perhaps become an important research agenda? (figure 2).

Acknowledgements I would like to express my sincere gratitude to my team members Velocity Hughes and Aleksandra Turkiewicz for providing helpful input on this editorial.

Contributors ME fully wrote this editorial.

Competing interests None declared.

Provenance and peer review Commissioned; externally peer reviewed.

CrossMark

To cite Englund M. *Ann Rheum Dis* 2018;**77**:159–161.

Linked

► http://dx.doi.org/10.1136/annrheumdis-2017-211172

Ann Rheum Dis 2018;**77**:159–161.
doi:10.1136/annrheumdis-2017-211664

REFERENCES

1 Sihvonen R, Paavola M, Malmivaara A, *et al*. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. *N Engl J Med* 2013;369:2515–24.
2 Sihvonen R, Paavola M, Malmivaara A, *et al*. Arthroscopic partial meniscectomy versus placebo surgery for a degenerative meniscus tear: a 2-year follow-up of the randomised controlled trial. *Ann Rheum Dis* 2017.
3 Harris I. *Surgery, the Ultimate Placebo: a Surgeon cuts through the evidence*: University of New South Wales Press, 2016.
4 Englund M, Guermazi A, Gale D, *et al*. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. *N Engl J Med* 2008;359:1108–15.
5 Zanetti M, Pfirrmann CW, Schmid MR, *et al*. Patients with suspected meniscal tears: prevalence of abnormalities seen on MRI of 100 symptomatic and 100 contralateral asymptomatic knees. *AJR Am J Roentgenol* 2003;181:635–41.
6 Neogi T, Felson D, Niu J, *et al*. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. *BMJ* 2009;339:b2844.
7 Kumm J, Roemer FW, Guermazi A, *et al*. Natural History of Intrameniscal Signal Intensity on Knee MR Images: Six Years of Data from the Osteoarthritis Initiative. *Radiology* 2016;278:164–71.

8 Englund M, Guermazi A, Roemer FW, *et al*. Meniscal tear in knees without surgery and the development of radiographic osteoarthritis among middle-aged and elderly persons: the Multicenter Osteoarthritis Study. *Arthritis Rheum* 2009;60:831–9.
9 Beaufils P, Becker R, Kopf S, *et al*. Surgical management of degenerative meniscus lesions: the 2016 ESSKA meniscus consensus. *Knee Surg Sports Traumatol Arthrosc* 2017;25:335–46.
10 Siemieniuk RAC, Harris IA, Agoritsas T, *et al*. Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *BMJ* 2017;357:j1982.
11 Bennell KL, Hinman RS, Metcalf BR, *et al*. Efficacy of physiotherapy management of knee joint osteoarthritis: a randomised, double blind, placebo controlled trial. *Ann Rheum Dis* 2005;64:906–12.
12 Bennell KL, Egerton T, Martin J, *et al*. Effect of physical therapy on pain and function in patients with hip osteoarthritis. *JAMA* 2014;311:1987–97.
13 Turkiewicz A, Timpka S, Thorlund JB, *et al*. Knee extensor strength and body weight in adolescent men and the risk of knee osteoarthritis by middle age. *Ann Rheum Dis* 2017.
14 Kise NJ, Risberg MA, Stensrud S, *et al*. Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up. *BMJ* 2016;354:i3740.
15 Juhl C, Christensen R, Roos EM, *et al*. Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials. *Arthritis Rheumatol* 2014;66:622–36.

The evolving role of the rheumatologist in the management of immune-related adverse events (irAEs) caused by cancer immunotherapy

Leonard Calabrese,[1] Xavier Mariette[2,3,4]

Handling editor Tore K Kvien

[1]Department of Rheumatology/Immunology, Cleveland Clinic, Cleveland, Ohio, USA
[2]Department of Rheumatology, Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, France
[3]Université Paris-Sud, Le Kremlin Bicêtre, France
[4]IMVA Center, INSERM, Le Kremlin Bicêtre, France

Correspondence to
Dr Leonard Calabrese, Department of Rheumatology/Immunology, Cleveland Clinic, Cleveland, OH 44195, USA; calabrl@ccf.org

LC and XM contributed equally.

Received 12 July 2017
Revised 5 September 2017
Accepted 8 September 2017
Published Online First 19 September 2017

ABSTRACT

The rapid introduction of immunotherapies for cancer-targeting immunological checkpoints has led to a new class of toxicities that appear to be of autoimmune and or autoinflammatory origin. These disorders are now referred to as immune-related adverse events (irAEs) and pose considerable challenges to patient care in terms of how to optimally manage these formidable toxicities while allowing effective antitumoural therapy to continue. While rheumatologists will naturally be called on to manage those irAEs of rheumatic origin, we believe there is a need and an opportunity for rheumatologists to participate as central figures in this evolving field, in large part because of our familiarity with multiorgan autoimmune disease and our expertise in crafting and utilising both traditional and biological immune-based therapies. Rheumatologists urgently need education in this evolving field to be best positioned as contributors to care of such patients and investigators of the underlying mechanisms of these complications.

The risk of immune-related adverse events (irAEs) secondary to cancer immunotherapy with checkpoint inhibitors has provided both a challenge and an opportunity for rheumatologists to engage meaningfully in the care and investigation of such patients. Our viewpoint is that not only do rheumatologists have much to add in terms of diagnostic and management skills for patients developing typical rheumatic complications (ie, arthritis, myositis, sicca syndrome, vasculitis) but we as a profession are, among all medical specialties, perhaps the best-equipped to manage the more complex strata of irAEs that can be life-threatening, involve multiple organ systems and at times evolve into chronic diseases.

By way of background, the six currently approved immune checkpoint inhibitors have added meaningfully to the care of patients with cancer; these agents have a broad range of activity demonstrating response rates of 15%–90% in more than 10 cancer types with the capacity to induce durable responses in select patients.[1] While the benefit to risk ratio of these agents is well established, the antitumour effects come at a cost: the generation of a unique spectrum of toxicities referred to as irAEs, including dermatologic, hepatic, endocrine, pulmonary and rheumatic complications.[2–5] It is not uncommon for checkpoint-treated patients to develop more than one irAE involving multiple organ systems.[6] While these complications are believed to arise due to off-target immunoenhancement of effector pathways,[7] they pose unique challenges and frequently require immunosuppressive regimens grounded in initial glucocorticoids, followed often by the addition of other non-biological or biological immunomodulators depending on the level of severity or persistence.[8] Moving ahead, it will also be critical to assess whether more aggressive immunosuppressive regimens will have deleterious effects on the antitumoural response for as of now some evidence suggests that the presence of irAEs in general and the use of glucocorticoids have not been deleterious.[9 10] Furthermore, in the absence of comparative effectiveness data in the overall management of irAEs, clinicians often craft specific regimens based on complex patient to patient considerations (ie, end organ involvement with tumour, previous immunosuppressive chemotherapy history, comorbidities and drug–drug interactions, etc). In general, these complications have been managed by oncologists guided by a general approach to toxicity management designed for ipilimumab (an anti-CTLA4), which was the first approved checkpoint inhibitor[11] and later by consensus opinion such as the USA-European collaborative for PD-1 agents.[12] Recently, a single centre has proposed a management algorithm for patients with immune-mediated inflammatory arthritis.[13] It is important to note that to date no randomised controlled trials in irAE management to determine if one strategy is superior to the other has been published. With this in mind, rheumatologists would appear well positioned to add meaningfully to the overall approach to irAEs, particularly in the following settings.

One of the greatest challenges in the growth of checkpoint therapy surrounds the question of whether patients with pre-existing autoimmune diseases, including conditions such as rheumatoid arthritis, other forms of inflammatory arthritis and various connective tissue diseases, are candidates for cancer immunotherapy; these patients were censored from early clinical trials. Given that in the USA alone, there may be upward of 50 million patients with some form of autoimmunity; this is a formidable problem.[14] To date, several small studies and anecdotal case reports examining the effects of checkpoint inhibition in patients with underlying autoimmunity, including rheumatic diseases, suggest that these types of patients can be effectively treated but flares of underlying diseases can and do occur in perhaps 1/3 of patients.[15–17] This issue is of particular importance as it can lead to an interruption in cancer treatment: when patients with underlying autoimmunity and cancer are treated with checkpoint inhibitors and experience a flare of their underlying disease, they may, as a

To cite: Calabrese L, Mariette X. *Ann Rheum Dis* 2018;**77**:162–164.

result, require increased immunosuppression; this added immunosuppression may prevent them from continuing their cancer immunotherapy until the underlying disease can be controlled. Clearly, maintaining their eligibility for continuing cancer immunotherapy must be the first priority, and rheumatologists can aid in this effort by collaborating on strategies that will allow this. Surely, from the patient's perspective, it can be reassuring to know that their specialist for their underlying autoimmune disease is actively engaged with their oncologist in the team's desire to defeat their cancer.

Another area of interest is predicting irAEs before they occur. While the early clinical series[3 18] of rheumatic irAEs failed to demonstrate the presence of autoantibodies in patients with inflammatory polyarthritis, several recent reports suggest that pre-existing autoantibodies such as anticitrullinated protein antibodies[5] and diabetes-associated islet antibodies[19] may be predictive of new-onset rheumatoid arthritis and type 1 diabetes. Thus, efforts to profile risk for incident irAEs prior to checkpoint therapy need to be explored and specialists such as rheumatologists may be logical partners to monitor and manage such complications before they occur.

Obviously, other specialties must be involved in the specific management of some of these IrAEs: neurologists, endocrinologists, internal medicine specialists, intensive care specialists, etc. We think that rheumatologists may be best equipped to orchestrate the management of these IrAEs since they are the specialists most closely and historically associated to immunology and mainly to immune treatment of systemic inflammatory diseases. Rheumatologists may also contribute meaningfully on the treatment team for the management of rare and occasionally life-threatening complications of critical end organs resulting in myocarditis[20] or central nervous system vasculitis[21] among others where prompt and effective immunosuppression is needed. Treatment algorithms[11 12] for common adverse events such as skin, bowel and liver endorse first-line glucocorticoids and drugs such as azathioprine, mycophenolate and short-term infliximab but do not explore other biological agents and strategies that may offer targeted therapy as our understanding of the underlying immunopathogenesis increases. A recent case report from the *New England Journal of Medicine*[22] exemplifies the need for more complex approaches to therapy, as they described a patient flaring with both Crohn's disease and psoriasis after treatment with a PD1 targeting agent who was treated with an anti-interleukin (IL)17 leading to exacerbation of the cancer. A more rational approach perhaps would have selected an antitumour necrosis factor (anti-TNF) agent with dual effects for both comorbidities. Of note, in a recent series of three cases, it was suggested that tocilizumab, an anti-IL6 receptor antibody, might be an effective alternative to corticosteroids or TNFα inhibitors for the treatment of arthritis irAEs.[23]

We believe this report merely demonstrates the need for more a sophisticated approach to the expanding spectrum of irAEs.

Finally, in terms of rheumatic complications such as inflammatory arthritis and connective tissue diseases, from early experience with small numbers of patients, it appears that these complications may be distinctive, for unlike virtually all other irAEs there is a high rate of chronicity with perhaps the majority of patients requiring ongoing therapy with biological and non-biological disease-modifying antirheumatic drugs. Thus, rheumatologists will inevitably be involved with the management of increasing numbers of oncology patients and engaging interprofessionally with oncologists moving forward.

The management of patients with cancer is undergoing a frame shift change with the introduction and expansion of checkpoint therapy which up until recently was only established in academic centres but now is rapidly spreading to community practices. New interprofessional relationships are needed to optimally manage increasing numbers of patients with irAEs and these oncology–rheumatology collaborations will be vital. We conclude by noting that numerous issues now challenge the rheumatology community in relationship to our evolving role in caring for patients with irAEs but an immediate challenge is how will we educate ourselves about this new area of medicine and new area of autoimmune disease? Merely encouraging rheumatologists to participate in the care of such patients is inadequate unless we strategise to educate ourselves on the rapidly expanding base of declarative and procedural knowledge that is essential to bring informed care to the patients and a new research agenda to address the evolving field.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Wolchok JD. PD-1 blockers. *Cell* 2015;162:937.
2 Cousin S, Italiano A. Molecular pathways: immune checkpoint antibodies and their toxicities. *Clin Cancer Res* 2016;22:4550–5.
3 Calabrese C, Kirchner E, Kontzias K, *et al*. Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity. *RMD Open* 2017;3:e000412.
4 Suarez-Almazor ME, Kim ST, Abdel-Wahab N, *et al*. Review: immune-related adverse events with use of checkpoint inhibitors for immunotherapy of cancer. *Arthritis Rheumatol* 2017;69:687–99.
5 Belkhir R, Burel SL, Dunogeant L, *et al*. Rheumatoid arthritis and polymyalgia rheumatica occurring after immune checkpoint inhibitor treatment. *Ann Rheum Dis* 2017;76:1747–50.
6 Zimmer L, Goldinger SM, Hofmann L, *et al*. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Cancer* 2016;60:210–25.
7 Huang AC, Postow MA, Orlowski RJ, *et al*. T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. *Nature* 2017;545:60–5.
8 Michot JM, Bigenwald C, Champiat S, *et al*. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer* 2016;54:139–48.
9 Schadendorf D, Wolchok JD, Hodi FS, *et al*. Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: a pooled analysis of randomized phase II and III trials. *J Clin Oncol* 2017:JCO.2017.73.228.
10 Horvat TZ, Adel NG, Dang TO, *et al*. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Oncol* 2015;33:3193–8.
11 Squibb B-M. Yervoy (Ipilimumab), immune-mediated adverse reaction management guide. 2011 http://www.yervoy.com/hcp/rems.aspx.
12 Weber JS, Postow M, Lao CD, *et al*. Management of adverse events following treatment with anti-programmed death-1 agents. *Oncologist* 2016;21:1230–40.
13 Naidoo J, Cappelli LC, Forde PM, *et al*. Inflammatory arthritis: a newly recognized adverse event of immune checkpoint blockade. *Oncologist* 2017;22:627–30.
14 Autoimmune Registry. Estimates of prevalence for autoimmune disease. http://www.autoimmuneregistry.org/autoimmune-statistics/.
15 Johnson DB, Sullivan RJ, Ott PA, *et al*. Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. *JAMA Oncol* 2016;2:234–40.
16 Menzies AM, Johnson DB, Ramanujam S, *et al*. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Ann Oncol* 2017;28:368–76.
17 Maul LV, Weichenthal M, Kähler KC, *et al*. Successful anti-PD-1 antibody treatment in a metastatic melanoma patient with known severe autoimmune disease. *J Immunother* 2016;39:188–90.

18 Cappelli LC, Gutierrez AK, Baer AN, *et al*. Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. *Ann Rheum Dis* 2017;76:43–50.
19 Godwin JL, Jaggi S, Sirisena I, *et al*. Nivolumab-induced autoimmune diabetes mellitus presenting as diabetic ketoacidosis in a patient with metastatic lung cancer. *J Immunother Cancer* 2017;5:40.
20 Johnson DB, Balko JM, Compton ML, *et al*. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med* 2016;375:1749–55.
21 Läubli H, Hench J, Stanczak M, *et al*. Cerebral vasculitis mimicking intracranial metastatic progression of lung cancer during PD-1 blockade. *J Immunother Cancer* 2017;5:46.
22 Esfahani K, Miller WH. Reversal of autoimmune toxicity and loss of tumor response by interleukin-17 blockade. *N Engl J Med* 2017;376:1989–91.
23 Kim ST, Tayar J, Trinh VA, *et al*. Successful treatment of arthritis induced by checkpoint inhibitors with tocilizumab: a case series. *Ann Rheum Dis* 2017;76:2061–4.

Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases

Jonathan Kay,[1] Monika M Schoels,[2] Thomas Dörner,[3] Paul Emery,[4] Tore K Kvien,[5] Josef S Smolen,[2,6] Ferdinand C Breedveld,[7] on behalf of the Task Force on the Use of Biosimilars to Treat Rheumatological Diseases

Handling editor David S Pisetsky

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-211937).

For numbered affiliations see end of article.

Correspondence to
Professor Jonathan Kay, Division of Rheumatology, Department of Medicine, UMass Memorial Medical Center and University of Massachusetts Medical School, Worcester, MA 01605, USA;
jonathan.kay@umassmemorial.org

JK and MMS contributed equally.

Received 15 June 2017
Revised 20 July 2017
Accepted 12 August 2017
Published Online First
3 October 2017

ABSTRACT

The study aimed to develop evidence-based recommendations regarding the evaluation and use of biosimilars to treat rheumatological diseases. The task force comprised an expert group of specialists in rheumatology, dermatology and gastroenterology, and pharmacologists, patients and a regulator from ten countries. Four key topics regarding biosimilars were identified through a process of discussion and consensus. Using a Delphi process, specific questions were then formulated to guide a systematic literature review. Relevant English-language publications through November 2016 were searched systematically for each topic using Medline; selected papers and pertinent reviews were examined for additional relevant references; and abstracts presented at the 2015 and 2016 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) annual scientific meetings were searched for those about biosimilars. The experts used evidence obtained from these studies to develop a set of overarching principles and consensus recommendations. The level of evidence and grade of recommendation were determined for each. By the search strategy, 490 references were identified. Of these, 29 full-text papers were included in the systematic review. Additionally, 20 abstracts were retrieved from the ACR and EULAR conference abstract databases. Five overarching principles and eight consensus recommendations were generated, encompassing considerations regarding clinical trials, immunogenicity, extrapolation of indications, switching between bio-originators and biosimilars and among biosimilars, and cost. The level of evidence and grade of recommendation for each varied according to available published evidence. Five overarching principles and eight consensus recommendations regarding the evaluation and use of biosimilars to treat rheumatological diseases were developed using research-based evidence and expert opinion.

INTRODUCTION

Treatment with biological agents (biologics) has dramatically improved the outcome for patients with inflammatory diseases. However, the high cost of these medications has limited access for many patients.[1] To make effective biologics more widely available, biosimilars of products that no longer are protected by patent have been developed and have been made available to patients at costs lower than those of the bio-originator. In the European Union (EU), the USA, Japan and other countries, biosimilars of adalimumab, etanercept, infliximab and rituximab have been approved, and those for which the bio-originator no longer is protected by patent have been marketed.

Over the past decade, several publications have examined the scientific, legal and regulatory aspects of biosimilar development.[1–6] However, little has been published to guide healthcare providers in critically evaluating and differentiating the scientific data available for each of these molecules. Thus, a multidisciplinary group was convened to develop consensus, at an international level, among patients and physicians regarding the evaluation and use of biosimilars to treat rheumatological diseases.

METHODS

Participants

An international multidisciplinary task force on biosimilars was convened in 2016, consisting of 25 experts from eight European countries, Japan and the USA (17 rheumatologists, 1 rheumatologist/regulator, 1 dermatologist, 1 gastroenterologist, 2 pharmacologists, 2 patients with rheumatic diseases as patients' representatives and 1 research fellow). The objective was to develop an evidence-based and consensus-based statement about the use of biosimilars to treat inflammatory diseases by identifying and critically appraising evidence in the literature. This statement was intended both to guide clinicians and to serve as a framework for future educational efforts.

Experts' consensus

In August 2016, a steering committee consisting of six rheumatologists and one research fellow, all of whom were members of this task force, held a preliminary meeting in Vienna, Austria. At this meeting, they identified four key topics for further discussion by the task force: issues related to clinical trials of biosimilars, extrapolation of indications, immunogenicity of biosimilars compared with their bio-originators, and switching between bio-originators and biosimilars and among biosimilars. Using a Delphi process, specific questions were formulated about these subjects to guide a systematic literature review (SLR), which was then performed to identify relevant publications through November 2016.

The Medline database was searched for English-language publications about biosimilars; selected papers and pertinent reviews were examined for additional relevant references. Abstracts presented at the 2015 and 2016 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) annual scientific

To cite: Kay J, Schoels MM, Dörner T, *et al*. *Ann Rheum Dis* 2018;**77**:165–174.

meetings were searched for those about biosimilars. The European public assessment reports for human medicines, published by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) publications (Drugs@FDA), were reviewed to identify those about biosimilars approved by the EMA and/or the FDA to treat rheumatological diseases, as of December 2016 (online supplementary table S1). The EU clinical trials register and ClinicalTrials.gov databases were queried to identify clinical trials in which a biosimilar was studied in patients with an inflammatory disease. We included publications on biosimilars that were approved to treat rheumatological diseases. During the initial search process, no quality criteria were applied for inclusion, but all relevant studies were later rated using the Oxford Centre for Evidence-Based Medicine Levels of Evidence 1.[7]

The findings of the SLR were communicated to the steering committee members, augmented by two pharmacologists and a rheumatologist/regulator, at a second meeting that was held in Leiden, the Netherlands, in December 2016. Additional presentations were made about the relative immunogenicity of biosimilars to their bio-originators and about regulatory issues related to approval of biosimilars by the EMA. Group discussion followed these talks, during which overarching principles and consensus statements were developed to propose to the entire task force.

On the following day, a consensus conference took place, at which all but two members of the full task force were in attendance. At this face-to-face meeting, a summary of the evidence obtained through the SLR was presented to the entire task force. Subsequently, the proposed overarching principles and consensus statements that had been developed by the augmented steering committee were presented. The task force members deliberated on each statement and modified the wording, if necessary. Each statement was then voted on and high-level agreement was achieved for all statements. The two members of the task force who were absent from the Leiden meeting subsequently voted on each statement by email and their votes were combined with those of the other task force members (table 1). Overarching principles and recommendations were accepted when ≥80% of the experts agreed.

RESULTS

Systematic literature review

The initial search strategy (online supplementary table S2) identified 490 publications in Medline, as of December 2016. After the selection process had been applied, 29 full-text papers were included. From the ACR and EULAR conference abstract databases, 20 abstracts were retrieved (online supplementary figure S1).

Experts' opinion approach

After discussing the results of the SLR, the consensus process was initiated. The full task force agreed on five overarching principles and eight consensus recommendations (table 1).

Table 1 Overarching principles (A–E) and consensus recommendations (1–8) for biosimilars

		Agreement* (%)	Level of evidence†	Grade of recommendation‡
Overarching principles				
A.	Treatment of rheumatic diseases is based on a shared decision-making process between patients and their rheumatologists.	100	5	D
B.	The contextual aspects of the healthcare system should be taken into consideration when treatment decisions are made.	100	5	D
C.	A biosimilar, as approved by authorities in a highly regulated area, is neither better nor worse in efficacy and not inferior in safety to its bio-originator.	88	5	D
D.	Patients and healthcare providers should be informed about the nature of biosimilars, their approval process, and their safety and efficacy.	96	5	D
E.	Harmonised methods should be established to obtain reliable pharmacovigilance data, including traceability, about both biosimilars and bio-originators.	100	5	D
Consensus recommendations				
1.	The availability of biosimilars must significantly lower the cost of treating an individual patient and increase access to optimal therapy for all patients with rheumatic diseases.	100	5	D
2.	Approved biosimilars can be used to treat appropriate patients in the same way as their bio-originators.	100	1b	A
3.	As no clinically significant differences in immunogenicity between biosimilars and their bio-originators have been detected, antidrug antibodies to biosimilars need not be measured in clinical practice.	100	2b	B
4.	Relevant preclinical and phase I data on a biosimilar should be available when phase III data are published.	100	5	D
5.	Since the biosimilar is equivalent to the bio-originator in its physicochemical, functional and pharmacokinetic properties, confirmation of efficacy and safety in a single indication is sufficient for extrapolation to other diseases for which the bio-originator has been approved.	100	5	D
6.	Currently available evidence indicates that a single switch from a bio-originator to one of its biosimilars is safe and effective; there is no scientific rationale to expect that switching among biosimilars of the same bio-originator would result in a different clinical outcome but patient perspectives must be considered.	96	1b	A
7.	Multiple switching between biosimilars and their bio-originators or other biosimilars should be assessed in registries.	100	5	D
8.	No switch to or among biosimilars should be initiated without the prior awareness of the patient and the treating healthcare provider.	91	5	D

*Agreement indicates percentage of experts who approved the recommendation during the final voting round of the consensus meeting.
†1a: systematic review of randomised clinical trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT; eg, <80% follow-up); 3a: systematic review of case–control studies; 3b: individual case–control study; 4: case-series (and poor quality cohort and case–control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.
‡A: based on consistent level 1 evidence; B: based on consistent level 2 or 3 evidence or extrapolations from level 1 evidence; C: based on level 4 evidence or extrapolations from level 2 or 3 evidence; D: based on level 5 evidence or on troublingly inconsistent or inconclusive studies of any level.

RECOMMENDATIONS

Five main topics related to biosimilars were identified: considerations regarding clinical trials, immunogenicity, extrapolation of indications, switching between bio-originators and biosimilars and among biosimilars, and cost. Within each of these areas, key issues were identified that form the basis for the overarching principles and consensus recommendations described here (table 1). We present the overarching principles and consensus statements in the sequence listed in table 1, followed by an explanatory discussion of each.

Overarching principles

Treatment of rheumatic diseases is based on a shared decision-making process between patients and their rheumatologists

A fundamental principle underlying the treatment of all diseases is that informed patients share in making decisions about therapy with their healthcare providers. For the rheumatic diseases, the rheumatologist is obliged to educate the patient both about the disease process and about appropriate treatment options. Once informed, the patient can then engage the healthcare provider in a dialogue in which personal preferences, treatment goals, and the potential risks and benefits of each treatment option are discussed and evaluated relative to one another. Such a discussion should result in optimal treatment of the disease process and empower patients to remain in control of their health.

The contextual aspects of the healthcare system should be taken into consideration when treatment decisions are made

The structure of healthcare systems varies in different countries. In some countries, the government oversees the healthcare system and serves as a single payer to cover the costs of medical treatment for its citizens. In other countries, such as the USA, a variety of systems are in place to support access to healthcare: some patients are covered by government-supported insurance plans, others purchase private insurance coverage, and some have no health insurance coverage at all. In single-payer systems, the payer often supports the cost of medications. However, in countries in which coverage for healthcare expenses is provided by a variety of systems, there often is a similar range of approaches to subsidise the cost of medications. Among those individuals who have prescription coverage, the proportion of the drug acquisition cost that is subsidised varies. Although only a small monetary copayment is required of some patients, others are expected to pay 20% or more of the cost of medications. This can place a significant burden on some individuals and may make necessary treatment inaccessible to some. These contextual aspects must be considered when choosing appropriate drug therapy for a given patient, since lower drug costs increase affordability.

A biosimilar, as approved by authorities in a highly regulated area, is neither better nor worse in efficacy and not inferior in safety to its bio-originator

A biosimilar is a replica of a biopharmaceutical that has met criteria for biosimilarity, according to a defined pathway established to demonstrate equivalent pharmacokinetics (PK), pharmacodynamics (PD) and efficacy and comparable safety and immunogenicity, and has been reviewed and approved by a regulatory authority in a highly regulated area. Many such regulatory agencies are members or observers of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).[8] ICH aims to recommend guidelines and requirements for approval of pharmaceutical products to achieve harmonisation among regulatory agencies worldwide.

The EMA defines a biosimilar as 'a biological medicinal product that contains a version of the active substance of an already authorised' bio-originator, for which 'similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy' has been demonstrated.[9] In the USA, a biosimilar is defined in the Biologics Price Competition and Innovation Act of 2009 as a biological product that is 'highly similar to the reference product notwithstanding minor differences in clinically inactive components' and that 'there are no clinically meaningful differences between the reference product and the biologic product in terms of the safety, purity and potency of the product'.[10] In 2005, the EMA proposed a pathway by which to approve similar biological products.[11] Five years later, the US Congress established a pathway for the approval of biological products that are 'highly similar' to their bio-originators.[10]

The regulatory pathways for approval of a biosimilar differ slightly between the EMA and the US FDA, but both follow a 'stepwise approach' and require extensive analytical studies followed by clinical studies comparing PK and PD parameters, immunogenicity, efficacy and safety of the proposed biosimilar to its bio-originator to confirm that there are 'no clinical meaningful differences' between the bio-originator and the biosimilar. The US FDA has articulated a 'totality of the evidence' approach to evaluating the accumulated data, in which all of the information is considered in its entirety without giving greater importance to any one aspect.[12] The EMA follows a similar process.[13] Many other countries have conformed to this approach and established comparable pathways to approve biosimilars.[3]

Biosimilarity is established, following a stepwise approach, by a series of comparative studies with high face validity. Analyses must demonstrate that the biosimilar and its bio-originator have the same primary amino acid sequence. Comparing multiple batches of a biosimilar candidate with many batches of its bio-originator, acquired over time, there must be no significant differences in charge isoforms, glycosylation, other post-translational modifications or impurities. There may be minor differences, but these must not affect critical quality attributes of the biologic. For therapeutic monoclonal antibodies, essential functional properties include Fc receptor binding, complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity, on which their mechanism of action may depend. Subsequent clinical studies must demonstrate PK and PD equivalence and equivalent efficacy in at least one disease for which the bio-originator is approved, as well as comparable safety and no greater immunogenicity of the biosimilar.

Because a biosimilar can rely on data generated for approval of its bio-originator, the clinical data required by regulatory pathways for biosimilar approval in the EU, the USA and most other countries are abbreviated, contrasted to those required for approval of bio-originators. PK typically is studied by comparing single doses of a biosimilar and its bio-originator in healthy subjects[14–20]; multiple dosing is subsequently assessed in patients.[21–24] Most regulatory agencies define PK equivalence of a biosimilar to its bio-originator as when the 90% CIs for the ratio of geometric means for area under the curve and maximal concentration between the biosimilar and its bio-originator fall within the log-transformed range of 80%–125% (±20%).[5 6] In published PK studies of approved biosimilar tumour necrosis factor (TNF) inhibitors, serum concentration time profiles of the biosimilar and its bio-originator have overlapped closely, and variability of the ratio of geometric means for PK parameters has been much less than that allowed by regulatory requirements.[7–12]

Phase III randomised controlled trials (RCTs) comparing the efficacy of a candidate biosimilar with its bio-originator should be conducted in a disease that is sensitive for detecting potential differences in efficacy between the biosimilar and its bio-originator. However, the same condition may not be the most sensitive in which to detect potential differences in safety, including immunogenicity. RCTs comparing a candidate biosimilar with its bio-originator should be of adequate duration to assess durability of response, safety and immunogenicity. These trials should use endpoints that are sensitive to detecting potential differences between a biosimilar and its bio-originator. Assessment of an outcome measure at early time points, during the rapid rise phase of the time–response curve, provides additional information.[25] Assessing response to treatment during the first 3 months allows comparison of the rapidity of onset. These issues must be taken into consideration when designing phase III RCTs comparing biosimilar with their bio-originators.

Since a phase III RCT comparing a biosimilar with its bio-originator is designed to demonstrate equivalence and aims to prove the null hypothesis, the primary analysis should be performed on the per protocol set.[26] Although an intention-to-treat analysis would bias towards the null hypothesis concluding that the two drugs are equivalent, secondary analyses should be performed on each endpoint using the intention-to-treat approach to account for possible differential dropout in the two treatment arms. The equivalence margin for RCTs comparing the efficacy of a biosimilar with its bio-originator is derived from a meta-analysis of the therapeutic effect of the bio-originator in the original placebo-controlled RCTs, calculated as the risk difference in the endpoint of interest between active drug and placebo. To preserve a proportion of the therapeutic effect of the bio-originator, the equivalence margin used in a comparative effectiveness RCT is usually half or less of the mean absolute difference derived in the meta-analysis.[19] Equivalence margins should be standardised for each bio-originator.[27] The EMA defines two-sided therapeutic equivalence in RCTs comparing a biosimilar with its bio-originator as when the 95% CI for the mean absolute difference in the primary endpoint between the biosimilar and its bio-originator falls within the predefined equivalence margin.[13] However, the US FDA prefers use of the narrower 90% CI to demonstrate therapeutic equivalence.[14]

A biosimilar that has satisfied the requirements of a dedicated pathway for regulatory approval will be neither better nor worse in efficacy and not inferior in safety to the various batches of the bio-originator. Since the processes for manufacturing biologics, including highly sensitive methods to assess quality, have matured over the past decades, major changes in the manufacturing process of the bio-originator are not likely and its efficacy and safety are unlikely to drift. Thus, efficacy and safety of a biosimilar can be expected to remain highly comparable to those of its bio-originator over time.

Patients and healthcare providers should be informed about the nature of biosimilars, their approval process, and their safety and efficacy

Given that biosimilars have only recently become available, many patients and healthcare providers are unfamiliar with this concept. Since biosimilars are usually marketed at a price lower than that of their bio-originators, some presume that biosimilars are of lesser quality. This misconception can and must be corrected by informing patients and healthcare providers about the nature of biosimilars, the rigorous approval process to which they are subjected by regulatory agencies, and the equivalent efficacy and comparable safety of approved biosimilars to their bio-originators.

Harmonised methods should be established to obtain reliable pharmacovigilance data, including traceability, about both biosimilars and bio-originators

During the development of a pharmaceutical product, a limited number of patients receive treatment with the investigational drug. Thus, it is important to gather safety and efficacy data after a drug has been approved and is commercially available. Especially since the clinical part of the development process for biosimilars is abbreviated relative to that for bio-originators, it is critical that postmarketing pharmacovigilance be conducted to confirm the efficacy and safety of a biosimilar over time in a much larger number of patients than were studied in RCTs.

Traceability is an issue for all drugs, not only for biosimilars. To facilitate postmarketing pharmacovigilance, the non-proprietary name of a biosimilar must be readily distinguishable from that of its bio-originator. In 2012, the WHO proposed that a unique four-letter 'biological qualifier' code be appended as a suffix to the core name. This nomenclature system would be applied retrospectively to the bio-originator and prospectively to designate biosimilars.[28] The US FDA has followed these WHO recommendations and, in 2017, issued guidance regarding non-proprietary naming of biological products, in which it specifies that the 'biological qualifier' code suffix consists of four lower-case letters and that it is unique and 'devoid of meaning'.[29] The five biosimilars approved in the USA to treat inflammatory diseases have been designated as adalimumab-adbm, adalimumab-atto, etanercept-szzs, infliximab-abda, and infliximab-dyyb. Similarly, a 'biological qualifier' code suffix will be appended retroactively to the core name of each bio-originator, so that these may be distinguished from biosimilars. This naming convention for biologics should facilitate traceability and allow effective postmarketing surveillance of the safety and efficacy of both biosimilars and their bio-originators. Within the European medicines regulatory network, pharmacovigilance is organised primarily at a national level in the Member States of the EU and the European Economic Area using brand names for postmarketing surveillance of both biosimilars and bio-originators. An advantage of using brand names is that these can be easily recalled and reported by both patients and their healthcare providers. Suspected adverse events are submitted to the EudraVigilance database, which allows monitoring safety of medications across the entire network. However, it is unfortunate that there has not yet been global agreement on nomenclature for all biologics. Regardless of the method used to distinguish among biosimilars and bio-originators, batch numbers are essential for tracing potential problems. However, although recorded by the dispensing pharmacist, batch numbers are infrequently noted by patients or healthcare providers and may be difficult to obtain when an adverse event occurs.

Consensus recommendations

The availability of biosimilars must significantly lower the cost of treating an individual patient and increase access to optimal therapy for all patients with rheumatic diseases

As the prevalence of chronic disease increases in both high-income and lower-income countries, pharmaceutical consumption must shift to lower cost products so as to improve access to all who need these medications.[30] An approved biosimilar should provide patients with an equivalent biologic at a cost lower than that of the bio-originator. Unlike a new medication, a biosimilar

of equivalent efficacy and comparable safety has no attribute other than price to distinguish it from its bio-originator.

The expenses associated with developing a biosimilar are but a fraction of those incurred during the development of a bio-originator. Thus, once patents for bio-originators have expired, the use of less expensive biosimilars should help to offset the necessary expense of using other medications to fulfil unmet therapeutic needs. Regardless, payers must transfer the savings realised from the reduced cost of developing a biosimilar back to the patient by improving access to treatment with lower copayments for medications or by lowering insurance premiums.[31]

A 2014 RAND Corporation study estimated the potential cost savings of biosimilars in the US market to be $44.2 billion over the subsequent decade, of which TNF inhibitors would account for 21% ($9.3 billion).[32] This study assumed that market competition would result in the price of a biosimilar being 35% lower than that of its bio-originator. However, at the time of the launch in September 2015 of filgrastim-sndz (Zarxio), the first biosimilar approved in the USA, its wholesale acquisition cost (WAC) was only 15% lower than that of bio-originator filgrastim.[33] Similarly, at the time of its launch in November 2016, the WAC of infliximab-dyyb (Inflectra) in the USA was only 15% lower than that of bio-originator infliximab.[34] However, discounts and ex-post rebates provided to third-party payers and pharmacy benefit management companies by bio-originator manufacturers might reduce or even eliminate the price differential between a biosimilar and its bio-originator. Small price differentials between biosimilars and bio-originators likely will decrease the market penetration of biosimilars and further reduce direct cost savings. A price discounted only 15% below that of the bio-originator may not be sufficient to motivate use of a biosimilar. Thus, to ensure market uptake of biosimilars, it is important that they be priced considerably lower than bio-originators.

In other countries, the price of biosimilars is lowest where market competition is greatest. In Canada, at the time of its launch in March 2015, the price of Inflectra was 34% lower than that of bio-originator infliximab.[35] The prices of biosimilars in the EU typically have been 20%–40% lower than those of the corresponding bio-originators, but this is much less than the 80% price reduction realised with generic small molecule drugs.[36] However, in Norway, where the national hospital system has a competitive tender process for the exclusive contracts to supply medications that are administered in-hospital, the tender accepted for Remsima in 2014 was 39% lower than that offered for bio-originator infliximab and that accepted in 2015 was 69% lower.[37] As expected, the market share of biosimilar infliximab is much larger in those countries where the price of the biosimilar is much lower than that of bio-originator infliximab.[38] The use of a tender system has important implications for maintaining a competitive environment and is likely to reduce both the price of biologics that no longer are protected by patent and that of biosimilars. However, such a system may also pose a threat to the level of market competition over the long term and might ultimately result in a market in which only one version of a biologics (biosimilar or bio-originator) is available (ie, 'winner-take-all').

In the EU5 (France, Germany, Italy, Spain and the UK), using a conservative budget impact model, the introduction of an etanercept biosimilar priced 10%–25% lower than bio-originator etanercept could yield net savings of €286 to €728 million over the subsequent 5 years.[39] Such savings could fund treatment with the biosimilar for many more patients. Presumably, the proportion of the cost of a biosimilar that is shared by the patient will be lower than that shared for a bio-originator. Thus, with more affordable drugs, patients may be more likely to adhere to their prescribed medication regimens. Moreover, in developing markets in which access to biologics is restricted by cost, the availability of a lower cost biosimilar might allow a patient to receive a treatment that previously was more difficult to obtain or unavailable. Thus, biosimilars should increase global access to effective treatments for inflammatory diseases.

Approved biosimilars can be used to treat appropriate patients in the same way as their bio-originators

Once a biosimilar has demonstrated high structural similarity and clinical equivalence to its bio-originator in a sensitive population and has been granted marketing authorisation, it can be considered to be essentially the same biologic as a new batch of the bio-originator. The finding of biosimilarity justifies use of an approved biosimilar in all the indications for which the bio-originator is authorised.

As no clinically significant differences in immunogenicity between biosimilars and their bio-originators have been detected, antidrug antibodies to biosimilars need not be measured in clinical practice

Antidrug antibodies (ADAs) typically develop in patients who are treated protractedly with biologics. Virtually all monoclonal antibodies induce an immune response with production of ADAs, often to the antigen-combining region (anti-idiotype antibodies).[40] ADAs bound to therapeutic monoclonal antibodies may form immune complexes which, when cleared by the reticuloendothelial system, result in lower trough drug concentrations and potentially decreased efficacy.[41] When the titre and affinity of ADAs for the biologic are high, the therapeutic effect is neutralised. Neutralising ADAs may be detected within 6 months after initial exposure to the biologic.[42]

Assays to detect ADAs have evolved over time to become more sensitive and specific.[41] Early studies of therapeutic monoclonal anti-TNF antibodies, using a bridging ELISA, identified ADAs in a small proportion of patients.[43] Subsequent studies have used assays that are less sensitive to drug interference, such as the homogeneous mobility shift assay method or the pH-shift anti-idiotype antigen-binding test, in which acid dissociation of drug–ADA complexes allows detection both of free ADAs and of those bound to drug.[44 45] In recent clinical trials, ADAs have been detected in a larger proportion of patients using the sensitive electrochemiluminescence bridging immunoassay.[46] However, the clinical relevance of ADAs, especially as to how they might differentiate biosimilars from their reference drugs, remains unclear.

The immunogenicity of a candidate biosimilar is best compared with that of its bio-originator in a clinical trial conducted in treatment-naïve patients.[12 47] These trials often have included a single crossover from the bio-originator to the candidate biosimilar. Thus far, such switches have not induced ADA formation. The proportion of subjects that develop ADAs to a biosimilar and to its bio-originator should be similar. Since neutralising ADAs are more clinically relevant, proportion of subjects developing these should also be reported.[48] If immunogenicity findings are to be extrapolated from a clinical trial in one disease to other indications, the patient population chosen for study should be that which is most likely to develop an immune response to the biologic.[12] Accordingly, patients not receiving concomitant immunosuppressive medications are preferred. However, in the clinical trials comparing the infliximab biosimilar CT-P13 with bio-originator infliximab, the prevalence of ADAs was higher in patients with rheumatoid arthritis receiving infliximab 3 mg/kg intravenously with concomitant methotrexate than in patients

with ankylosing spondylitis receiving infliximab 5 mg/kg as monotherapy.[21 46] Thus, genetic factors, the underlying disease process and the dose of the biologic administered may be more important than concomitant immunosuppressive medications in determining the predisposition to develop ADAs.

Although not typically measured in clinical practice by rheumatologists, trough drug concentrations provide a more relevant, indirect comparative assessment of immunogenicity between a biosimilar and its bio-originator than does detection of ADAs. As no clinically significant differences in immunogenicity between biosimilars and their bio-originators have been detected, ADAs to biosimilars need not be measured in clinical practice.[49 50] However, the assessment of immunogenicity should not be dismissed completely, as it is a useful measure for active pharmacovigilance. Evaluating comparative immunogenicity data, acquired in both clinical and postmarketing studies of biosimilars, should help to increase confidence in using biosimilars among healthcare providers.[51]

Relevant preclinical and phase I data on a biosimilar should be available when phase III data are published

As substantial emphasis has been placed on analytical and PK comparisons in the development of biosimilars, preclinical analytical data and phase 1 PK data should be available in peer-reviewed journals when data from phase III RCTs are published. Data from relevant physicochemical, in vitro functional and PK studies of a biosimilar should be published before or simultaneously with those from the phase III comparative effectiveness RCT. Physicochemical and in vitro functional data comparing the biosimilar with its bio-originator have been published in peer-reviewed journals for the infliximab biosimilar SB2, the etanercept biosimilars SB4 and GP 2015, and the adalimumab biosimilar ABP 501.[52–56] For the infliximab biosimilar CT-P13, selected physicochemical and in vitro functional data were published as supplementary data in appendices to the primary publications reporting the results of the phase I and phase III studies that compared CT-P13 with bio-originator infliximab.[21 46]

Phase I PK data comparing biosimilars with their bio-originators have usually been published in a peer-reviewed journal before or simultaneously with publication of the results of the phase III study in manuscript form. Results of the phase I PK study comparing ABP 501 with bio-originator adalimumab were published before publication of a manuscript reporting the phase III data.[18 57] Similarly, results of the phase I PK study comparing SB2 with bio-originator infliximab were published before the phase III study was published,[17 58] and results of the phase I PK study comparing SB4 with bio-originator etanercept were published before the phase III study was published.[19 59] The phase I and phase III studies comparing CT-P13 with bio-originator infliximab,[21 46] and those comparing GP2015 with bio-originator etanercept both were published simultaneously.[20 60] The availability of this information, when the phase III RCT data are published, facilitates assessment of biosimilarity based on a 'totality-of-the-evidence' approach.[61]

Since the biosimilar is equivalent to the bio-originator in its physicochemical, functional and pharmacokinetic properties, confirmation of efficacy and safety in a single indication is sufficient for extrapolation to other diseases for which the bio-originator has been approved

Based on the extensive historical clinical experience with the bio-originator in each of its licensed indications, regulatory agencies allow efficacy and safety data for a biosimilar to be extrapolated from one approved indication to others in which the biosimilar has not been studied, if the mechanism of action of the bio-originator is considered to be the same in each disease.[62 63] The comprehensive preclinical comparison of the biosimilar to its bio-originator, in which their similarity is confirmed by many different analytical and functional assays, forms the basis for this 'extrapolation of indications.' Thus, after having demonstrated efficacy and safety equivalent to its bio-originator in at least one RCT conducted in patients with a disease for which the bio-originator is authorised, a biosimilar may apply for approval in any or all indications for which its bio-originator already has been authorised without an RCT in each indication.

By this process, biosimilars have usually been granted marketing authorisation in all indications for which the bio-originator has been approved but in which the biosimilar has not been studied. In this context, experts from national and international organisations have argued that convincing data from RCTs are needed for each individual indication.[64–72] However, biosimilars have always demonstrated efficacy equivalent to that of their bio-originators when studied in more than one indication.[21 46 73 74] Also, the biosimilar infliximab, CT-P13, has exhibited efficacy and safety comparable to bio-originator infliximab in several small, prospective case series of patients with indications for which approval had been based on extrapolation of data from the RCTs.[75–78] Although Health Canada initially denied the biosimilar infliximab CT-P13 extrapolation of data from clinical trials conducted in patients with rheumatoid arthritis and ankylosing spondylitis to inflammatory bowel diseases, this decision was ultimately reversed by the same regulatory authority.[79] Nonetheless, biosimilars have demonstrated efficacy and safety when used in clinical practice to treat approved indications in which they had not been studied in comparison to their bio-originators.[78]

Currently available evidence indicates that a single switch from a bio-originator to one of its biosimilars is safe and effective; there is no scientific rationale to expect that switching among biosimilars of the same bio-originator would result in a different clinical outcome but patient perspectives must be considered

Switching patients from bio-originators to their biosimilars and from one biosimilar to another should be evidence-based. Current data suggest that treating a patient with an approved biosimilar should yield results comparable to those achieved when the patient is treated with the bio-originator. However, no study to date has evaluated the efficacy or safety of switching between different biosimilars of the same bio-originator.

Ideally, the consequences of switching from a bio-originator to a biosimilar should be compared with that of continued treatment with the bio-originator in an RCT, conducted in patients who are receiving stable treatment with the bio-originator. Extensions to phase III RCTs of several biosimilars, in which subjects treated initially with the bio-originator were switched to the biosimilar, have been published.[80–84] Observing no loss of efficacy and no increase in the rate of adverse events following this single switch supports making this switch in clinical practice, only if the biosimilar costs less than the bio-originator. However, if a patient has failed to respond to a specific biologic, a biosimilar of that product should not subsequently be prescribed.

An RCT was conducted in Norway to assess the effect of switching from bio-originator infliximab (Remicade) to the biosimilar infliximab CT-P13 on efficacy and safety in the various indications for which both had been approved. NOR-SWITCH was a 52-week, double blind, non-inferiority, phase IV RCT that

enrolled 482 patients with a variety of diseases: Crohn's disease (n=155), ulcerative colitis (n=93), spondyloarthritis (n=91), rheumatoid arthritis (n=78), psoriasis (n=35) and psoriatic arthritis (n=30), each of whom had been on stable treatment with bio-originator infliximab for at least 6 months.[78] The primary endpoint was worsening in disease-specific composite measures and/or agreement between the investigator and the patient that increased disease activity required a change in treatment by week 52. This study demonstrated non-inferiority of switching from the bio-originator to the biosimilar, using a non-inferiority margin of 15%, as compared with continuation of treatment with the bio-originator for the aggregate of subjects with the various diseases enrolled. However, NOR-SWITCH was not powered to compare these two treatment strategies in subjects with any individual disease. Similar proportions of patients in each group developed treatment-emergent adverse events (TEAEs), serious adverse events and TEAEs resulting in study drug discontinuation, and the prevalence and incidence of ADAs, as well as trough drugs levels, were similar between the two groups. Thus, NOR-SWITCH supports the practice of switching patients with stable disease activity from bio-originator infliximab to the biosimilar CT-P13. However, these results cannot be generalised to other biologics and their biosimilars or to frequent switching back-and-forth between bio-originator and biosimilar. For each new biosimilar and application device, an RCT should be conducted to evaluate safety and continued efficacy after switching from the bio-originator or to another biosimilar. However, once sufficient experience has been gained, additional switching studies may no longer be necessary.

Even if data from RCTs support the practice of switching from a bio-originator to its biosimilar or between biosimilars, patients must feel comfortable receiving the treatment that they have been prescribed. To achieve this, rheumatologists should inform patients about the rigorous development process during which biosimilars have been assessed and shown to be highly similar to their bio-originators. Patient perspectives must be taken into account. Patients should understand that an approved biosimilar may be like another batch of its bio-originator and should provide similar therapeutic benefit with comparable safety. They also should be informed about the economic implications of switching, which should allow more patients to benefit from treatment with biologics. However, if some patients remain uneasy about switching from the bio-originator to a biosimilar, even with this information, their preferences must be considered when making a therapeutic decision.

Multiple switching between biosimilars and their bio-originators or other biosimilars should be assessed in registries

Substitution, in which a biosimilar is prescribed in place of its bio-originator, must be distinguished from interchangeability, wherein someone other than the prescribing healthcare provider initiates the switch from bio-originator to biosimilar or between two biosimilars. Of note, in the EU, the term 'substitution' implies what is considered in the USA to be 'interchange'. Thus, terminology must be harmonised worldwide. In the EU, the EMA does not have the authority to designate a biosimilar as being interchangeable; rather, this judgement must be made by regulatory agencies in each Member State.[85]

To support the designation of interchangeability, an RCT that incorporates multiple switches between the two biologics must be conducted. The US FDA has issued draft guidance on demonstrating interchangeability of a biosimilar with its bio-originator, in which it suggests that postmarketing pharmacovigilance data should be combined with data from at least one prospective RCT that compares repeated switching between the bio-originator and the biosimilar to continuous treatment with the bio-originator.[86] Subjects in the 'switching arm' of such a study switch at least three times between the bio-originator and the biosimilar, whereas subjects in the 'non-switching arm' continue treatment with only the bio-originator. After the last switch from the bio-originator to the biosimilar, subjects in the 'switching arm' should remain on the biosimilar. The primary endpoints for such a study should be PK parameters; secondary endpoints should evaluate efficacy, safety and immunogenicity. However, to date, no biosimilar has been evaluated according to this study design.

Systematic postmarketing pharmacovigilance should be carried out using biologics registries and by conducting long-term, observational cohort studies to which data are reported regularly by prescribing healthcare providers and patients who are treated with specific products. Biologics registries in many countries have provided insight into the short-term and long-term safety of biologics.[87–93] Data collected about the use of biosimilars should be integrated into these existing biologics registries. Pertinent standardised data must be collected to address any remaining uncertainty regarding the safety of biosimilars. Although not designed primarily to assess efficacy, the durability or potential loss of efficacy after switching from a bio-originator to its biosimilar might become evident in such a registry.

No switch to or among biosimilars should be initiated without the prior awareness of the patient and the treating healthcare provider

Patients with rheumatological diseases may be reluctant to switch medications, even when their disease remains active, because of fear of disease worsening or of developing an adverse effect on a new medication.[94] However, the concern that therapeutic efficacy might be lost after switching from a bio-originator to its biosimilar has not been supported by currently available data.

In the EU, the introduction of infliximab and etanercept biosimilars has generated market competition, which has resulted in price reductions for their reference products and for the other bio-originator TNF inhibitors.[38] Patients and their healthcare providers share the responsibility to consider equity when choosing a course of treatment and must consider cost in the decision-making process. However, in some countries, the choice of biologic is often imposed by payers rather than being made by either the patient or his or her treating healthcare provider.

Transparency is of utmost importance in the therapeutic relationship between a patient and his or her healthcare provider. Therapeutic decisions must be made jointly by the patient in consultation with the healthcare provider. As with all changes in treatment, the patient and the healthcare provider should be fully aware of any change and should agree with its implementation.

CONCLUSION

The differing opinions about biosimilars that have been published by various national and international medical subspecialty organisations illustrate the lack of confidence shared by many clinicians regarding the appropriate use of biosimilars.[64–72 95–98] However, a rapidly growing body of evidence has begun to reduce residual uncertainty about their use. This consensus statement aims to raise awareness about biosimilars and to discuss the key issues that healthcare providers must consider when using biosimilars to treat their patients. The assembled group of experts and patients achieved a high level of agreement about the evaluation of biosimilars and their use to treat rheumatological diseases.

The participants were confident that biosimilars approved by authorities in a highly regulated area are unlikely to differ from their bio-originators in clinically meaningful ways. Nevertheless, given the complex nature of all biopharmaceuticals, the treating clinician must be the only one to decide whether to prescribe a biosimilar in place of a bio-originator on a case-by-case basis with full awareness of the patient. The group believed that adequate evidence exists to support the decision to switch from a biologic, which no longer is protected by patent, to its biosimilar. In addition, the group concluded that there is sufficient evidence about safety and efficacy of biosimilars to allow for extrapolation of indications. However, there remained concern about switching between two biosimilars or between a bio-originator and its biosimilar on multiple occasions because adequate studies have not yet been conducted to assess these circumstances. To facilitate making informed decisions about therapeutic substitution with biosimilars, healthcare providers are encouraged to gather pharmacovigilance data in registries about the outcome of such switches made in the context of clinical practice. Data available as of December 2016 support the use of biosimilars by rheumatologists to encourage a fair and competitive market for biologics. Biosimilars now provide an opportunity to expand access to effective but expensive medications, increasing the number of available treatment choices and helping to control rapidly increasing drug expenditures.

Author affiliations
[1]Division of Rheumatology, Department of Medicine, UMass Memorial Medical Center and University of Massachusetts Medical School, Worcester, Massachusetts, USA
[2]Department of Internal Medicine, Centre for Rheumatic Diseases, Hietzing Hospital, Vienna, Austria
[3]Department of Medicine/Rheumatology and Clinical Immunology, Charité Universitätsmedizin and Deutsches Rheumaforschungszentrum (DRFZ), Berlin, Germany
[4]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Leeds, UK
[5]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
[6]Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria
[7]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

Correction notice This article has been corrected since it published Online First. The collaborators statement has been added.

Collaborators Members of the Task Force on the Use of Biosimilars to Treat Rheumatologic Diseases: Johannes W J Bijlsma, Jürgen Braun, Vivian P Bykerk, Silvio Danese, Maarten P T de Wit, João Goncalves, Tom W J Huizinga, John D Isaacs, Arthur F Kavanaugh, Pekka Kurki, Thomas A Luger, Ulf Müller-Ladner, Karel Pavelkam, Huub Schellekens, Anja Strangfeld, Tsutomu Takeuchi, Marieke Voshaar and Michael H Weisman.

Contributors MMS performed the systematic literature review. JK drafted the manuscript with advice from FCB, TD, PE, TKK and JSS. FCB, TD, PE, JK, TKK and JSS were involved in conceiving the study. All authors were involved in analysing and interpreting data and in producing the recommendations, and all have reviewed and approved the final manuscript.

Funding This study was funded by an unrestricted educational grant from Amgen.

Competing interests JK has received research grants paid to his institution from AbbVie, Eli Lilly and Company, Genentech, Pfizer and UCB, and has provided expert advice to AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb Company, Crescendo Bioscience, Eli Lilly and Company, Epirus Biopharmaceuticals, Merck Sharp & Dohme, Pfizer, Samsung Bioepis, Sandoz, Roche Laboratories and UCB. TD has received research grants or iDMC honoraria paid to his institution from AbbVie, Ablynx, AstraZeneca, Bristol-Myers Squibb Company, Celgene, GlaxoSmithKline, Samsung Bioepis, Roche Laboratories, Sanofi and UCB, and has provided expert advice to and/or had speaking engagements for AbbVie, Ablynx, Amgen, AstraZeneca, Biogen, Bristol-Myers Squibb Company, Celgene, Epirus Biopharmaceuticals, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer/Hospira, Samsung Bioepis, Roche Laboratories, Sanofi and UCB. PE has received research grants paid to his institution from and has provided expert advice to AbbVie, Bristol-Myers Squibb Company, Eli Lilly and Company, Merck Sharp & Dohme, Novartis, Pfizer, Samsung Bioepis, Sandoz, Roche Laboratories and UCB. TKK has received research grants paid to his institution from AbbVie, Bristol-Myers Squibb Company, Merck Sharp & Dohme, Pfizer/Wyeth, Roche Laboratories and UCB, and has provided expert advice to and/or had speaking engagements for AbbVie, Amgen, Biogen, Bristol-Myers Squibb Company, Celltrion Healthcare, Epirus Biopharmaceuticals, Merck Serono SA, Merck Sharp & Dohme, Mundipharma, Orion, Pfizer/Hospira, Pfizer/Wyeth, Samsung Bioepis, Sandoz, Roche Laboratories and UCB. JSS has received research grants paid to his institution from AbbVie, Eli Lilly and Company, Janssen Biotech, Merck Sharp & Dohme, Pfizer and Roche Laboratories, and has provided expert advice to and/or had speaking engagements for AbbVie, Amgen, AstraZeneca, Astro; Bristol-Myers Squibb Company, Celgene, Celltrion Healthcare, Chugai, Eli Lilly and Company, Gilead, GlaxoSmithKline, ILTOO, Janssen Biotech, Medimmune, MSD, Novartis-Sandoz, Pfizer, Roche Laboratories, Samsung Bioepis, Sanofi and UCB. FCB has provided expert advice to and/or had speaking engagements for AbbVie, Amgen, Epirus Biopharmaceuticals, Merck Sharp & Dohme and Pfizer.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Kay J. Biosimilars: a regulatory perspective from America. *Arthritis Res Ther* 2011;13:112.
2 Kay J, Feagan BG, Guirguis MS, *et al*. Health Canada/BIOTECanada Summit on regulatory and clinical topics related to subsequent entry biologics (biosimilars), Ottawa, Canada, 14 May 2012. *Biologicals* 2012;40:517–27.
3 Scheinberg MA, Kay J. The advent of biosimilar therapies in rheumatology--"O brave new world". *Nat Rev Rheumatol* 2012;8:430–6.
4 Dörner T, Strand V, Castañeda-Hernández G, *et al*. The role of biosimilars in the treatment of rheumatic diseases. *Ann Rheum Dis* 2013;72:322–8.
5 Dörner T, Kay J. Biosimilars in rheumatology: current perspectives and lessons learnt. *Nat Rev Rheumatol* 2015;11:713–24.
6 Dörner T, Strand V, Cornes P, *et al*. The changing landscape of biosimilars in rheumatology. *Ann Rheum Dis* 2016;75:974–82.
7 OCEBM Levels of Evidence Working Group. Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009). 2009 http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/ (accessed 18 Jul 2017).
8 The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH official website. 2017 http://www.ich.org/ (accessed 28 Jan 2017).
9 Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products. 2014 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf (accessed 20 Nov 2016).
10 Biologics Price Competition and Innovation Act of 2009. *United States Code. 111th Congress*. 2nd Session edn. United States, 2010:804–21.
11 Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products. 2005 http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf (accessed 20 Nov 2016).
12 US Food & Drug Administration. Guidance for industry. Scientific considerations in demonstrating biosimilarity to a reference product. 2015 http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf (accessed 22 Jun 2016).
13 Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2014 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf (accessed 10 Nov 2016).
14 Gu N, Yi S, Kim TE, *et al*. Comparative pharmacokinetics and tolerability of branded etanercept (25 mg) and its biosimilar (25 mg): a randomized, open-label, single-dose, two-sequence, crossover study in healthy Korean male volunteers. *Clin Ther* 2011;33:2029–37.
15 Yi S, Kim SE, Park MK, *et al*. Comparative pharmacokinetics of HD203, a biosimilar of etanercept, with marketed etanercept (Enbrel®): a double-blind, single-dose, crossover study in healthy volunteers. *BioDrugs* 2012;26:177–84.
16 Park W, Lee SJ, Yun J, *et al*. Comparison of the pharmacokinetics and safety of three formulations of infliximab (CT-P13, EU-approved reference infliximab and the US-licensed reference infliximab) in healthy subjects: a randomized, double-blind, three-arm, parallel-group, single-dose, Phase I study. *Expert Rev Clin Immunol* 2015;11(Suppl 1):25–31.
17 Shin D, Kim Y, Kim YS, *et al*. A randomized, Phase I pharmacokinetic study comparing SB2 and Infliximab reference product (Remicade(®)) in healthy subjects. *BioDrugs* 2015;29:381–8.
18 Kaur P, Chow V, Zhang N, *et al*. A randomised, single-blind, single-dose, three-arm, parallel-group study in healthy subjects to demonstrate pharmacokinetic equivalence of ABP 501 and adalimumab. *Ann Rheum Dis* 2017;76:526–33.

19 Park W, Yoo DH, Jaworski J, *et al*. Comparable long-term efficacy, as assessed by patient-reported outcomes, safety and pharmacokinetics, of CT-P13 and reference infliximab in patients with ankylosing spondylitis: 54-week results from the randomized, parallel-group PLANETAS study. *Arthritis Res Ther* 2016;18:25.
20 von Richter O, Skerjanec A, Afonso M, *et al*. GP2015, a proposed etanercept biosimilar: Pharmacokinetic similarity to its reference product and comparison of its autoinjector device with prefilled syringes. *Br J Clin Pharmacol* 2017;83:732–41.
21 Park W, Hrycaj P, Jeka S, *et al*. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann Rheum Dis* 2013;72:1605–12.
22 Takeuchi T, Yamanaka H, Tanaka Y, *et al*. Evaluation of the pharmacokinetic equivalence and 54-week efficacy and safety of CT-P13 and innovator infliximab in Japanese patients with rheumatoid arthritis. *Mod Rheumatol* 2015;25:817–24.
23 Cohen S, Emery P, Greenwald M, *et al*. A phase I pharmacokinetics trial comparing PF-05280586 (a potential biosimilar) and rituximab in patients with active rheumatoid arthritis. *Br J Clin Pharmacol* 2016;82:129–38.
24 Yoo DH, Suh CH, Shim SC, *et al*. A multicentre randomised controlled trial to compare the pharmacokinetics, efficacy and safety of CT-P10 and innovator rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2017;76:566–70.
25 Kay J, Smolen JS. Biosimilars to treat inflammatory arthritis: the challenge of proving identity. *Ann Rheum Dis* 2013;72:1589–93.
26 Rutherford AI, Galloway JB. Biosimilars in rheumatology: out of the laboratory and into practice. *Expert Rev Clin Immunol* 2016;12:697–9.
27 Kay J, Isaacs JD. Clinical trials of biosimilars should become more similar. *Ann Rheum Dis* 2017;76:4–6.
28 World Health Organization Programme on International Nonproprietary Names (INN). Biological qualifier: An INN proposal. 2014 http://www.who.int/medicines/services/inn/bq_innproposal201407.pdf (accessed 18 Nov 2016).
29 US Food & Drug Administration. Guidance for industry: Nonproprietary naming of biological products. 2017 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf (accessed 27 Jan 2017).
30 Hoebert J, Laing R, Stephens P. *The world medicines situation 2011: pharmaceutical consumption*. Geneva, Switzerland: World Health Organization, 2011:1–17.
31 MacDougall D, Crowell K, Prager S, *et al*. IMS health white paper: biosimilars: who saves? 2016 https://structurecms-staging-psyclone.netdna-ssl.com/client_assets/dwonk/media/attachments/57dc/387d/6970/2d6c/ad6f/0000/57dc387d69702d6cad6f0000.pdf?1474050173 (accessed 25 Feb 2017).
32 Mulcahy AW, Predmore Z, Mattke S. The cost savings potential of biosimilar drugs in the United States. Perspectives. 2014 http://www.rand.org/pubs/perspectives/PE127.html (accessed 18 Nov 2016).
33 Raedler LA, Zarxio RLA. Zarxio (Filgrastim-sndz): First Biosimilar Approved in the United States. *Am Health Drug Benefits* 2016;9:150–4.
34 Pfizer IncPfizer announces the U.S. availability of biosimilar INFLECTRA® (infliximab-dyyb). Company to begin shipping to wholesalers in late November, 2016Pfizer Inc, 2016 New York, NY. http://www.pfizer.com/news/press-release/press-release-detail/pfizer_announces_the_u_s_availability_of_biosimilar_inflectra_infliximab_dyyb (accessed 7 Jan 2017).
35 Canadian Drug Expert Committee. CDEC final recommendation: Infliximab (Inflectra - Hospia Healthcare Corporation). Common Drug Review. 2014 https://www.cadth.ca/media/cdr/complete/cdr_complete_SE0384_Inflectra_Dec-23-14.pdf (accessed 7 Jan 2017).
36 Haustein R, *et al*. Saving money in the European healthcare systems with biosimilars. *GaBI J* 2012;1:120–6.
37 Mack A. Norway, biosimilars in different funding systems. What works? *GaBI J* 2015;4:90–2.
38 IMS Health. *The impact of biosimilar competition*. London, UK: IMS Health Inc., 2016:1–30.
39 Ruff L, Rezk MF, Uhlig T, *et al*. Budget impact analysis of an etanercept biosimilar for the treatment of all licensed etanercept indications for adults in Europe. *Value Health* 2015;18:A639.
40 van Schouwenburg PA, van de Stadt LA, de Jong RN, *et al*. Adalimumab elicits a restricted anti-idiotypic antibody response in autoimmune patients resulting in functional neutralisation. *Ann Rheum Dis* 2013;72:104–9.
41 van Schouwenburg PA, Rispens T, Wolbink GJ. Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. *Nat Rev Rheumatol* 2013;9:164–72.
42 Bartelds GM, Krieckaert CL, Nurmohamed MT, *et al*. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. *JAMA* 2011;305:1460–8.
43 Lipsky PE, van der Heijde DM, St Clair EW, *et al*. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000;343:1594–602.
44 van Schouwenburg PA, Krieckaert CL, Rispens T, *et al*. Long-term measurement of anti-adalimumab using pH-shift-anti-idiotype antigen binding test shows predictive value and transient antibody formation. *Ann Rheum Dis* 2013;72:1680–6.
45 Wang S-L, Hauenstein S, Ohrmund L, *et al*. Monitoring of adalimumab and antibodies-to-adalimumab levels in patient serum by the homogeneous mobility shift assay. *J Pharm Biomed Anal* 2013;78-79:39–44.
46 Yoo DH, Hrycaj P, Miranda P, *et al*. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis* 2013;72:1613–20.
47 Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. 2012 https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf (accessed 20 Nov 2016).
48 Shankar G, Devanarayan V, Amaravadi L, *et al*. Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products. *J Pharm Biomed Anal* 2008;48:1267–81.
49 Ben-Horin S, Yavzori M, Benhar I, *et al*. Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. *Gut* 2016;65:1132–8.
50 Ruiz-Argüello MB, Maguregui A, Ruiz Del Agua A, *et al*. Antibodies to infliximab in Remicade-treated rheumatic patients show identical reactivity towards biosimilars. *Ann Rheum Dis* 2016;75:1693–6.
51 Gonçalves J, Araújo F, Cutolo M, *et al*. Biosimilar monoclonal antibodies: preclinical and clinical development aspects. *Clin Exp Rheumatol* 2016;34:698–705.
52 Hong J, Lee Y, Lee C, *et al*. Physicochemical and biological characterization of SB2, a biosimilar of Remicade® (infliximab). *MAbs* 2017;9:365–83.
53 Cho IH, Lee N, Song D, *et al*. Evaluation of the structural, physicochemical, and biological characteristics of SB4, a biosimilar of etanercept. *MAbs* 2016;8:1136–55.
54 Hofmann HP, Kronthaler U, Fritsch C, *et al*. Characterization and non-clinical assessment of the proposed etanercept biosimilar GP2015 with originator etanercept (Enbrel(®)). *Expert Opin Biol Ther* 2016;16:1185–95.
55 Liu J, Eris T, Li C, *et al*. Assessing analytical similarity of proposed Amgen biosimilar ABP 501 to adalimumab. *BioDrugs* 2016;30:321–38.
56 Velayudhan J, Chen YF, Rohrbach A, *et al*. Demonstration of functional similarity of proposed biosimilar ABP 501 to adalimumab. *BioDrugs* 2016;30:339–51.
57 Cohen S, Genovese MC, Choy E, *et al*. Efficacy and safety of the biosimilar ABP 501 compared with adalimumab in patients with moderate to severe rheumatoid arthritis: a randomised, double-blind, phase III equivalence study. *Ann Rheum Dis* 2017;76:1679–87.
58 Choe JY, Prodanovic N, Niebrzydowski J, *et al*. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2017;76:58–64.
59 Emery P, Vencovský J, Sylwestrzak A, *et al*. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2017;76:51–7.
60 Griffiths CEM, Thaçi D, Gerdes S, *et al*. The EGALITYch study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis. *Br J Dermatol* 2017;176:928–38.
61 Kozlowski S, Woodcock J, Midthun K, *et al*. Developing the nation's biosimilars program. *N Engl J Med* 2011;365:385–8.
62 US Food & Drug Administration. Guidance for industry. Biosimilars: questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009. 2015 http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm444661.pdf (accessed 31 Oct 2016).
63 Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2006 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003920.pdf (accessed 20 Nov 2016).
64 Argüelles-Arias F, Barreiro-de-Acosta M, Carballo F, *et al*. Joint position statement by "Sociedad Española de Patología Digestiva" (Spanish Society of Gastroenterology) and "Sociedad Española de Farmacología" (Spanish Society of Pharmacology) on biosimilar therapy for inflammatory bowel disease. *Rev Esp Enferm Dig* 2013;105:37–43.
65 Danese S, Gomollon F. Governing Board and Operational Board of ECCO. ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD). *J Crohns Colitis* 2013;7:586–9.
66 Gecse KB, Khanna R, van den Brink GR, *et al*. Biosimilars in IBD: hope or expectation? *Gut* 2013;62:803–7.
67 Danese S, Fiorino G, Michetti P. Viewpoint: knowledge and viewpoints on biosimilar monoclonal antibodies among members of the European Crohn's and Colitis Organization. *J Crohns Colitis* 2014;8:1548–50.
68 Fiorino G, Danese S. The biosimilar road in inflammatory bowel disease: the right way? *Best Pract Res Clin Gastroenterol* 2014;28:465–71.
69 Fiorino G, Girolomoni G, Lapadula G, *et al*. The use of biosimilars in immune-mediated disease: A joint Italian Society of Rheumatology (SIR), Italian Society of Dermatology

(SIDeMaST), and Italian Group of Inflammatory Bowel Disease (IG-IBD) position paper. *Autoimmun Rev* 2014;13:751–5.
70 Hlavaty T, Letkovsky J. Biosimilars in the therapy of inflammatory bowel diseases. *Eur J Gastroenterol Hepatol* 2014;26:1–587.
71 Schreiber S, Luger T, Mittendorf T, *et al*. [Evolution of biologicals in inflammation medicine--biosimilars in gastroenterology, rheumatology and dermatology]. *Dtsch Med Wochenschr* 2014;139:2399–404.
72 Committee on Rheumatologic Care. American College of Rheumatology position statement: Biosimilars. 2016 http://www.rheumatology.org/Portals/0/Files/Biosimilars-Position-Statement.pdf (accessed 20 Nov 2016).
73 Cohen SB, Genovese MC, Choy EH, *et al*. Randomized, double-blind, Phase 3 study of efficacy and safety of ABP 501 compared with adalimumab in subjects with moderate to severe rheumatoid arthritis [abstract]. *Arthritis Rheumatol* 2015;67(suppl 10() http://acrabstracts.org/abstract/randomized-double-blind-phase-3-study-of-efficacy-and-safety-of-abp-501-compared-with-adalimumab-in-subjects-with-moderate-to-severe-rheumatoid-arthritis/.
74 Papp K, Bachelez H, Costanzo A, *et al*. Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: A randomized, double-blind, multicenter, phase III study. *J Am Acad Dermatol* 2017;76:1093–102.
75 Nikiphorou E, Kautiainen H, Hannonen P, *et al*. Clinical effectiveness of CT-P13 (Infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. *Expert Opin Biol Ther* 2015;15:1677–83.
76 Benucci M, Gobbi FL, Bandinelli F, *et al*. Safety, efficacy and immunogenicity of switching from innovator to biosimilar infliximab in patients with spondyloarthritis: a 6-month real-life observational study. *Immunol Res* 2017;65:419-422.
77 Gentileschi S, Barreca C, Bellisai F, *et al*. Switch from infliximab to infliximab biosimilar: efficacy and safety in a cohort of patients with different rheumatic diseasesResponse to: Nikiphorou E, Kautiainen H, Hannonen P, et al. Clinical effectiveness of CT-P13 (Infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. Expert Opin Biol Ther. 2015;15:1677-1683. *Expert Opin Biol Ther* 2016;16:1311–2.
78 Jørgensen KK, Olsen IC, Goll GL, *et al*. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet* 2017;389:2304–16.
79 Health Canada. Regulatory decision summary INFLECTRA. 2016 http://www.hc-sc.gc.ca/dhp-mps/prodpharma/rds-sdr/drug-med/rds-sdr-infectra-184564-eng.php (accessed 29 Sep 2016).
80 Kay J, Wyand M, Chandrashekara S, *et al*. BOW015, a biosimilar infliximab, in patients with active rheumatoid arthritis on stable methotrexate doses: 54-week results of a randomized, double-blind, active comparator study [abstract]. *Arthritis Rheumatol* 2014;66:3538.
81 Weinblatt ME, Baranauskaite A, Niebrzydowski J, *et al*. Sustained efficacy and comparable safety and immunogenicity after transition to SB5 (an adalimumab biosimilar) vs. continuation of SB5 or reference adalimumab (Humira®) in patients with rheumatoid arthritis: Results of phase III study [abstract]. 2016 http://acrabstracts.org/abstract/sustained-efficacy-and-comparable-safety-and-immunogenicity-after-transition-to-sb5-an-adalimumab-biosimilar-vs-continuation-of-sb5-or-reference-adalimumab-humira-in-patients-with-rheumatoi/ (accessed 7 Jan 2017).
82 Park W, Yoo DH, Miranda P, *et al*. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. *Ann Rheum Dis* 2017;76:346–54.
83 Yoo DH, Prodanovic N, Jaworski J, *et al*. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. *Ann Rheum Dis* 2017;76:355–63.
84 Emery P, Vencovský J, Sylwestrzak A, *et al*. Long-term efficacy and safety in patients with rheumatoid arthritis continuing on SB4 or switching from reference etanercept to SB4. *Ann Rheum Dis* 2017;76:1986–91.
85 Thimmaraju PK, Rakshambikai R, Farista R, *et al*. Legislations on biosimilar interchangeability in the US and EU – developments far from visibility. GaBI Online - Generics and Biosimilars Initiative 2015. 2015 http://www.gabionline.net/Sponsored-Articles/Legislations-on-biosimilar-interchangeability-in-the-US-and-EU-developments-far-from-visibility (accessed 20 Nov 2016).
86 Food US, Administration D. Guidance for industry: Considerations in demonstrating interchangeability with a reference product, draft guidance. 2017 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery (accessed 17 Jan 2017).
87 Gómez-Reino JJ, Carmona L, Angel Descalzo M, *et al*. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis Rheum* 2007;57:756–61.
88 Askling J, van Vollenhoven RF, Granath F, *et al*. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? *Arthritis Rheum* 2009;60:3180–9.
89 Greenberg JD, Reed G, Kremer JM, *et al*. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. *Ann Rheum Dis* 2010;69:380–6.
90 Salmon-Ceron D, Tubach F, Lortholary O, *et al*. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. *Ann Rheum Dis* 2011;70:616–23.
91 Sakai R, Komano Y, Tanaka M, *et al*. Time-dependent increased risk for serious infection from continuous use of tumor necrosis factor antagonists over three years in patients with rheumatoid arthritis. *Arthritis Care Res* 2012;64:1125–34.
92 Zink A, Manger B, Kaufmann J, *et al*. Evaluation of the RABBIT Risk Score for serious infections. *Ann Rheum Dis* 2014;73:1673–6.
93 Mercer LK, Galloway JB, Lunt M, *et al*. BSRBR Control Centre Consortium. Risk of lymphoma in patients exposed to antitumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann Rheum Dis* 2017;76:497–503.
94 Wolfe F, Michaud K. Resistance of rheumatoid arthritis patients to changing therapy: discordance between disease activity and patients' treatment choices. *Arthritis Rheum* 2007;56:2135–42.
95 Fonseca JE, Gonçalves J, Araújo F, *et al*. The Portuguese Society of Rheumatology position paper on the use of biosimilars. *Acta Reumatol Port* 2014;39:60–71.
96 Abad Hernández MÁ, Andreu JL, Caracuel Ruiz MÁ, *et al*. Position paper from the Spanish Society of Rheumatology on biosimilar drugs. *Reumatol Clin* 2015;11:269–78.
97 Azevedo VF, Meirelles ES, Kochen JA, *et al*. Recommendations on the use of biosimilars by the Brazilian Society of Rheumatology, Brazilian Society of Dermatology, Brazilian Federation of Gastroenterology and Brazilian Study Group on Inflammatory Bowel Disease--Focus on clinical evaluation of monoclonal antibodies and fusion proteins used in the treatment of autoimmune diseases. *Autoimmun Rev* 2015;14:769–73.
98 British Society for Rheumatology. Position statement on biosimilar medicines (Revised January 2017). 2017 http://www.rheumatology.org.uk/includes/documents/cm_docs/2017/r/revised_bsr_biosimilars_position_statement_jan_2017.pdf (accessed 14 Mar 2017).

Novel therapies for immune-mediated inflammatory diseases: What can we learn from their use in rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and ulcerative colitis?

Kenneth F Baker,[1,2] John D Isaacs[1,2]

Handling editor Tore K Kvien

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-211555).

[1]Musculoskeletal Research Group and Arthritis Research UK Centre of Excellence in Rheumatoid Arthritis Pathogenesis, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK
[2]Newcastle NIHR Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University, Newcastle upon Tyne, UK

Correspondence to
Professor John D Isaacs, Musculoskeletal Research Group, Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, William Leech Building, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK; john.isaacs@ncl.ac.uk

Received 29 March 2017
Revised 31 May 2017
Accepted 1 July 2017
Published Online First 1 August 2017

ABSTRACT

The past three decades have witnessed remarkable advances in our ability to target specific elements of the immune and inflammatory response, fuelled by advances in both biotechnology and disease knowledge. As well as providing superior treatments for immune-mediated inflammatory diseases (IMIDs), such therapies also offer unrivalled opportunities to study the underlying immunopathological basis of these conditions.

In this review, we explore recent approaches to the treatment of IMIDs and the insights to pathobiology that they provide. We review novel biologic agents targeting the T-helper 17 axis, including therapies directed towards interleukin (IL)-17 (secukinumab, ixekizumab, bimekizumab), IL-17R (brodalumab), IL-12/23p40 (ustekinumab, briakinumab) and IL-23p19 (guselkumab, tildrakizumab, brazikumab, risankizumab, mirikizumab). We also present an overview of biologics active against type I and II interferons, including sifalumumab, rontalizumab, anifrolumab and fontolizumab. Emerging strategies to interfere with cellular adhesion processes involved in lymphocyte recruitment are discussed, including both integrin blockade (natalizumab, vedolizumab, etrolizumab) and sphingosine-1-phosphate receptor inhibition (fingolimod, ozanimod). We summarise the development and recent application of Janus kinase (JAK) inhibitors in the treatment of IMIDs, including first-generation pan-JAK inhibitors (tofacitinib, baricitinib, ruxolitinib, peficitinib) and second-generation selective JAK inhibitors (decernotinib, filgotinib, upadacitinib). New biologics targeting B-cells (including ocrelizumab, veltuzumab, tabalumab and atacicept) and the development of novel strategies for regulatory T-cell modulation (including low-dose IL-2 therapy and Tregitopes) are also discussed. Finally, we explore recent biotechnological advances such as the development of bispecific antibodies (ABT-122, COVA322), and their application to the treatment of IMIDs.

INTRODUCTION

Rapid progress in both disease knowledge and biotechnology over the past three decades has led to an increasingly diverse armamentarium of therapies for immune-mediated inflammatory diseases (IMIDs). As well as providing better and more focused therapies, these novel approaches can provide unique insights into disease pathogenesis or, indeed the complications of therapy. An early example was the recognition of the central importance of tumour necrosis factor-α (TNF-α) in granuloma maintenance, and hence protection against reactivation of latent tuberculosis.[1] In this review, we discuss recent approaches to the treatment of IMIDs, with a particular focus on biological and biotechnological advances, and examine the insights that they provide.

THE TH17 AXIS

CD4+ T cells sit at the interface between innate and adaptive immunity, and are considered the orchestrators of the adaptive immune response. Early studies of CD4+ T-cell biology described two mutually exclusive phenotypes, T-helper (Th)1 and Th2. Th1 cells promote cellular immunity against intracellular pathogens via the release of cytokines such as interferon gamma (IFN-γ), whereas Th2 cells promote humoral immunity and the response to helminth infections via the production of interleukin (IL)-4, IL-5 and IL-13.[2] Th1 cells were initially regarded as the drivers of many IMIDs, including rheumatoid arthritis (RA), although both animal and human data suggested that they were not always essential, catalysing the search for alternative subsets.[3] Th17 cells appeared to fill this gap, at least in some diseases. IL-17, one of the cytokines produced by this subset, is a potent pro-inflammatory cytokine which, together with TNF-α and IL-1β, recruits neutrophils as well as inhibiting chondrocyte metabolism and promoting osteoclastogenesis.[2] Since their discovery, Th17 cells have been implicated in a variety of IMIDs including RA, psoriasis, psoriatic arthritis (PsA), ankylosing spondylitis (AS) and inflammatory bowel disease.[4] Blocking the Th17 axis, either by inhibiting IL-17 directly or via preventing Th17 cell differentiation, is now an area of intense therapeutic development (figure 1).[5]

Strategies to block IL-17

IL-17 comprises a family of six homologous cytokines (IL-17A to F), of which IL-17A is the most abundant, most potent and best characterised.[6] Homodimers and heterodimers of IL-17 cytokines signal via dimeric IL-17 receptors, of which there are five identified subunits (IL-17RA to E).[6] The precise binding affinity, cellular distribution and downstream action of the various IL-17 receptors are yet to be fully elucidated. Nevertheless, it

To cite: Baker KF, Isaacs JD. *Ann Rheum Dis* 2018;**77**:175–187.

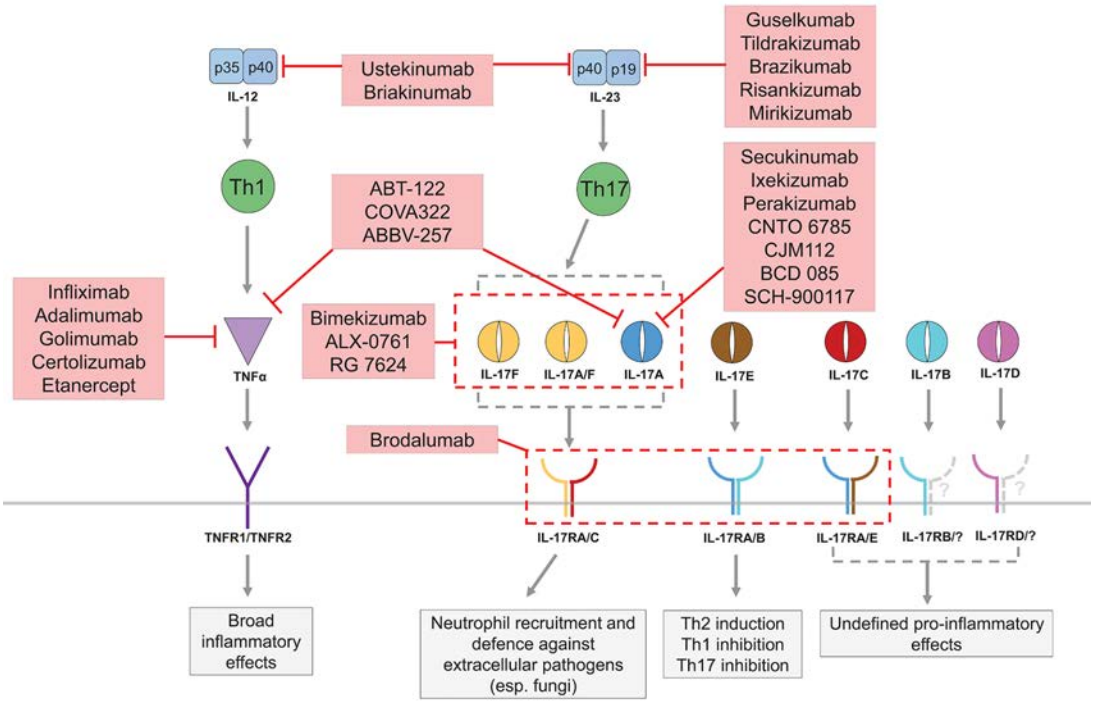


Figure 1 Overview of biologics targeted against elements of the T-helper (Th)17/interleukin (IL)-17 and tumour necrosis factor-α (TNF-α) axes. Adapted from Bartlett and Million[5] and Beringer *et al*.[6]

is apparent that blockade of different IL-17 cytokines or their receptors can yield quantitatively and qualitatively different therapeutic responses.

Secukinumab is a fully human monoclonal antibody (mAb) against IL-17A, and is effective in the treatment of plaque psoriasis, PsA and AS,[7] although has proved disappointing in the treatment of RA.[8] Ixekizumab, a humanised anti-IL-17A mAb, has similarly shown efficacy to date in psoriasis[9] and PsA.[10] In PsA trials, articular efficacy of IL-17 blockade is similar to TNF blockade (and superior to effects in RA), whereas skin efficacy is clearly superior to that of TNF blockade.[9] More recently bimekizumab, a humanised mAb directed against a homologous epitope shared between both IL-17A and IL-17F, has shown promising results in early phase clinical trials in psoriasis[11] and PsA.[12] Other biologics that neutralise both IL-17A and F, including true bispecific antibodies (see the 'Newer technologies' section), are currently in development (table 1). Blockade of IL-17 is associated with the development of candidiasis, which is not generally severe, but highlights the importance of IL-17 in fungal defence.

In addition to cytokine neutralisation, IL-17 inhibition can be achieved by blocking the IL-17 receptor. Brodalumab is a human mAb against IL-17RA, which is required for formation of the dimeric receptors necessary for IL-17A, IL-17F, IL-17A/F, IL-17C and IL-17E (IL-25) signalling.[13] Brodalumab thus exerts a much broader blockade of IL-17 signalling than the targeting of specific cytokines (figure 1). Nevertheless, the inhibition of IL-17E, which promotes a Th2 response while potentially inhibiting Th17 differentiation in mice,[14] and in human IBD[15] and RA,[16] could be therapeutically counterproductive in some disease settings. As discussed by Patel and Kuchroo,[3] this may explain the lack of effect of brodalumab in RA,[17] despite modest efficacies of secukinumab[18] and ixekizumab.[19] Brodalumab is licensed for the treatment of psoriasis in Japan and the USA, and will shortly receive European marketing authorisation.

Similar to RA, IL-17 blockade appears to have limited efficacy in non-infective uveitis.[3] These observations highlight that the presence of a cytokine in diseased tissue does not necessarily equate to an irreplaceable role in pathogenesis. Furthermore, both secukinumab[20] and brodalumab[21] have been demonstrated to worsen Crohn's disease (CD). Thus, in contrast to its pro-inflammatory role in other diseases and locations, IL-17A may function as a negative regulator of immunity in the gut mucosa, perhaps via interaction with fungal elements of the intestinal microbiome.[22 23] This observation is important in view of the clinical overlap between seronegative IMIDs, for example, trials of IL-17 blockade in psoriasis were associated with haemorrhagic diarrhoea as an adverse reaction.[24] In addition, concerns surrounding a possible association between brodalumab and suicidal ideation have hampered the development of this drug,[25] although these concerns may have been overstated.[26]

Th17 differentiation and the IL-12 superfamily

Central to the polarisation of naïve CD4+ T cells to distinct effector phenotypes are members of the IL-12 cytokine superfamily, namely IL-12, IL-23, IL-27 and IL-35.[27] These cytokines and their receptors also exist as dimers with considerable sequence homology between subunits, although with often opposing roles in immunity. Increasing knowledge of the constituent components of this family, particularly IL-12 and −23, has brought opportunities for therapeutic intervention aimed at blocking pathogenic Th17 differentiation[28] (figure 1, table 1).

Ustekinumab is a fully human mAb against the p40 subunit common to IL-12 and IL-23, licensed for the treatment of psoriasis, PsA and CD.[29] It has also shown benefit in AS in an open-label study[30] and a separate post hoc pooled analysis.[31] Intriguingly, and in direct contrast to IL-17A blockade, ustekinumab is effective in CD with evidence for a prolonged benefit following a single infusion.[32 33] Paradoxically, ustekinumab was inferior to secukinumab in moderate-to-severe psoriasis with a comparable safety profile.[34] These contrasting observations demonstrate first that blocking Th17 differentiation via IL-23

Table 1 Development of biologics active against Th17 pathway targets

Biologic agent	Developer	Psoriasis	PsA	AS	RA	IBD	Other indications
Anti-IL-17A mAb							
Secukinumab [AIN457, KB03303A] (*Consentyx*)	Novartis	Marketed	Marketed	Marketed	P-III	Discontinued (CD)	Alopecia areata (P-II) Atopic dermatitis (P-II)
Ixekizumab [LY2439821] (*Taltz*)	Eli Lily	Marketed	P-III (submitted)	P-III	P-II		
CNTO 6785	Janssen, MorphoSys				P-II		COPD (P-II)
CJM112	Novartis	P-I/II					Acne (P-II) Hydradenitis suppurativa (P-II)
BCD 085	Biocad	P-II		P-II			
SCH-900117	Merck & Co				P-I		
Perakizumab [RG 4934, RO 5310074]	Roche		Discontinued				
Dual anti-IL-17A and anti-IL-17F mAb							
Bimekizumab [CDP-4940, UCB-4940]	UCB	P-II	P-II	P-II	P-II	P-II (UC)	
ALX-0761 [MSB-0010841, M-1095]	Merck Serono, Ablynx	P-I					
RG 7624 [NI-1401, MCAF-5352A]	Genentech, NovImmune SA	Preclinical					
Dual IL-17A and TNF-α mAb							
ABT-122	AbbVie		P-II		P-II		
COVA322	Janssen	P-I/II					
ABBV-257	AbbVie				P-I		
LY 3114062*	Eli Lilly						'Inflammatory arthritis' (P-I)
Anti-IL-17RA mAb							
Brodalumab [AMG 827, KHK4827] (*Lumicef*, *Siliq*, *Kyntheum*)	AstraZeneca, Kyowa Hakko Kirin, Valeant Pharmaceuticals, LEO Pharma	Marketed	Marketed†	P-III	Discontinued	Discontinued (CD)	
Anti-IL-12/23p40 mAb							
Ustekinumab [CNTO-1275] (*Stelara*)	Janssen	Marketed	Marketed	P-III	Discontinued	Marketed (CD) P-III (UC)	SLE (P-II) Atopic dermatitis (P-II)
Briakinumab [ABT-874, A-796874.0, BSF415977, J695, LU415977, WAY-165772] (*Ozespa*)	Abbott	P-III (submission withdrawn)			Discontinued	Discontinued (CD)	
Anti-IL-23 mAb							
Guselkumab [CNTO-1959]	Janssen, MorphoSys	P-III (submitted)	P-II		P-II		
Tildrakizumab [SCH-900222, MK-3222]	Merck, Sun Pharmaceutical Industries	P-III (submitted)	P-II	P-II			

Continued

Table 1 Continued

Biologic agent	Developer	Psoriasis	PsA	AS	RA	IBD	Other indications
Brazikumab [AMG 139, MEDI2070]	Allergan, AstraZeneca, Amgen					P-II (CD)	
Risankizumab [ABBV 066, BI 655066]	Boehringer Ingelheim, AbbVie	P-III	P-II	P-II		P-II (CD)	Asthma (P-II)
Mirikizumab [LY 3074828]	Eli Lilly	P-II				P-II (CD and UC)	

Adapted from Refs 4 6 122 123. Development status based on http://adisinsight.springer.com, accessed 30 May 2017.
*LY3114062 mechanism of action is not yet disclosed, but believed to be a dual IL-17/TNF-α inhibitor.
†Brodalumab approved for treatment of psoriatic arthritis in Japan, although currently not approved for this indication in USA or Europe.
AS, ankylosing spondylitis; CD, Crohn's disease; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; IL, interleukin; P-I, phase I clinical trial; P-II, phase II clinical trial; P-III, phase III clinical trial; PsA, psoriatic arthritis; mAb, monoclonal antibody; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; Th, T-helper; TNF, tumour necrosis factor; UC, ulcerative colitis.

inhibition is mechanistically distinct from the blockade of IL-17A itself, and second that the relative effects differ between diseases.

It is also possible to selectively inhibit IL-23 by targeting its unique p19 subunit, and numerous such mAbs are in development for the treatment of psoriasis and IBD (figure 1, table 1). Purported advantages of selective IL-23 inhibition over dual IL-12/IL-23 blockade include the potential for less severe infections and lower malignancy risk; indeed, postmarketing data in psoriasis suggest an increased risk of non-melanoma skin cancer with ustekinumab, which may be a consequence of inhibition of IL-12-mediated cellular immunity.[35] Whether these theoretical advantages translate to clear benefits in the long term awaits confirmation.

Head-to-head trials in psoriasis

As illustrated above, head-to-head trials in psoriasis have been particularly illuminating with regard to the relative dominance of pathogenic pathways in this condition. For example, both IL-17A blockade with ixekizumab[9] and IL-23 blockade with guselkumab[36] are superior to TNF-α blockade (with etanercept and adalimumab, respectively). In other trials, IL-17A blockade with secukinumab,[34] IL-17R blockade with brodalumab[37] and IL-23p19 blockade with risankizumab[38] all appear superior to IL-12/23p40 blockade with ustekinumab. IL-17A, IL-17A/F, IL-17R and IL-23p19 blockade look similarly effective in these various trials, although, as in CD, IL-23p19 blockade appears to have particularly long-lasting efficacy.

The reason for the distinct effects of IL-12/23p40 versus IL-17 blockade is not immediately apparent, particularly the contrasting effects in different diseases. However, Th17 cells produce cytokines other than IL-17A (eg, IL-17F and IL-22), and IL-17A is also produced by cellular subtypes other than Th17 cells. These are less influenced by IL-23 family signalling, and in some environments (eg, the gut), IL-17 may even have regulatory functions.[4 23] Furthermore, IL-12/23p40 blockade also inhibits IL-12 signalling, a pro-Th1 cytokine which plays a key role in the pathogenesis of CD.[39] It is therefore apparent that simultaneous blockade of multiple cytokines, or blockade of the same immune axis at different hierarchical levels, can produce different outcomes dependent on the tissue and disease context in which it is deployed.

Summary: blocking the IL-17 axis—what have we learnt?

In summary, IL-17 is a key pathogenic cytokine in multiple IMIDs. However, its mere presence does not necessarily imply a dominant pathogenic role. Furthermore in a single condition, such as PsA, its relative role may vary between tissues. Lastly, blocking the axis at distinct levels can have differing effects, with distinct hierarchies in different diseases.

THE TYPE I IFN AXIS

IFNs are a family of potent immunostimulatory cytokines that are broadly divided into three subtypes: type I (IFN-α, β, ε, κ and ω), type II (IFN-γ) and the newly characterised type III (IFN-λ)[40] (figure 2). Of all the type I IFNs (IFN-I), IFN-α is the most abundant and best characterised, and exists in 13 distinct although homologous subtypes.[40] IFN-I production is tightly regulated such that levels are virtually undetectable in health. However, during pro-inflammatory states, such as viral infections, IFN-I is rapidly produced in large quantities.[41] Especially notable in their propensity to secrete IFN-I are plasmacytoid dendritic cells (pDCs), which abundantly express intracellular pattern recognition receptors such as toll-like receptor (TLR)-7

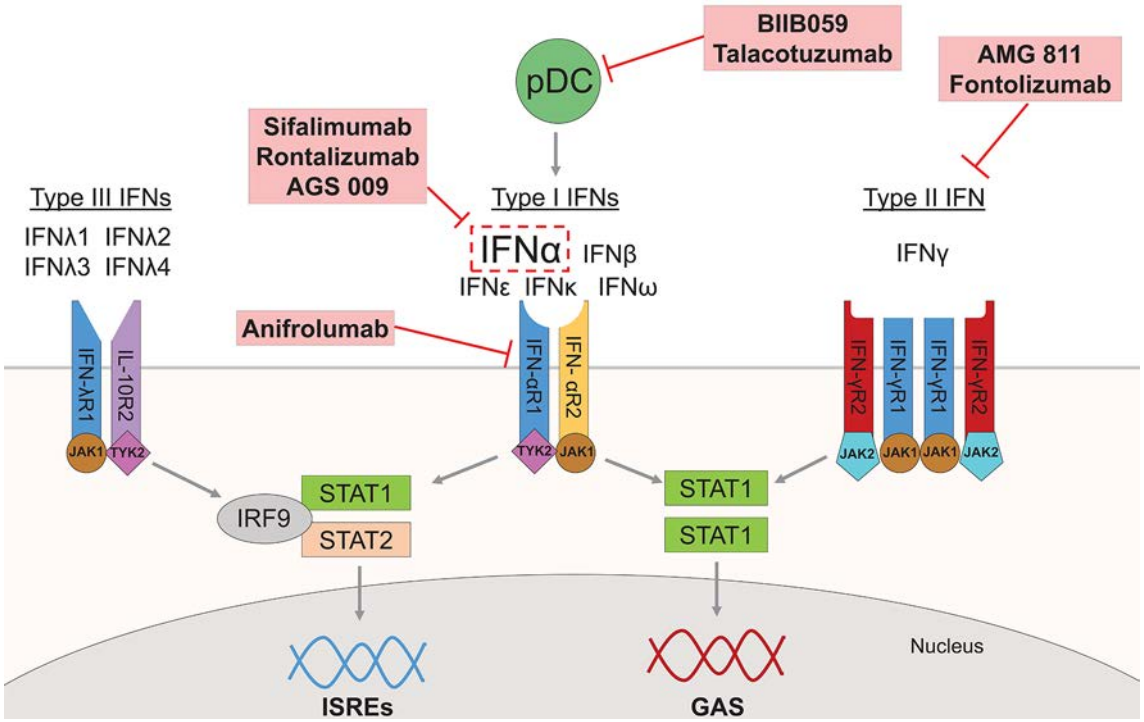


Figure 2 Overview of biologics targeted against interferon (IFN) pathways. GAS, interferon-γ activated site; IRF9, interferon regulatory factor 9; ISREs, interferon-stimulated response elements; JAK1/2, Janus kinase 1/2; pDC, plasmacytoid dendritic cell; STAT1/2, signal transducer and activator of transcription 1/2; TYK2, tyrosine kinase 2. Adapted from Oon *et al*.[44]

and TLR-9.[42] On ligation of the IFN-I receptor (IFNAR), IFN-I induces the upregulated expression of a stereotypical set of genes, known as IFN-stimulated genes (ISGs).[40] The effects of IFN-I are vigorously pro-inflammatory and include dendritic cell maturation and activation, Th1 and Th17 polarisation, reduced regulatory T cells (Treg) function and increased B-cell activation and subsequent antibody production.[41]

The role of IFN in autoimmunity is highlighted by observations of lupus-like autoimmunity arising de novo in patients receiving treatment with IFN-α for malignancy and chronic viral hepatitis.[43] Furthermore, the ISGs are upregulated in several disease states, most notably systemic lupus erythematosus (SLE), where their expression correlates with more severe disease. They are also upregulated in primary Sjögren's syndrome, systemic sclerosis and a subset of patients with RA.[41] Indeed, the potent IFN-I production by pDCs observed following TLR-7/9 ligation by endogenous nucleic acid complexes provides a potential mechanistic basis to explain the provenance of the cytokine in the pathogenesis of SLE, where therapeutic strategies to block the IFN-I pathway are currently in development (see online supplementary Table S1).[44]

Blocking IFN-α signalling

Sifalimumab is a fully human mAb against multiple IFN-α subtypes, especially IFN-α6, IFN-2b and IFN-2a,[45] and has shown promise in a recent phase IIb clinical trial in SLE. In this study,[46] 431 patients were randomised to receive either monthly infusions of sifalimumab or placebo in addition to standard care. While the trial just missed its primary end point across dosing groups, the highest dose was statistically superior to placebo. As predicted, there was a trend towards a greater effect in patients with a high IFN gene signature.[46] Consistent with the role of IFN-α in viral immunity, herpes zoster infections were increased in the sifalimumab group in a dose-dependent manner. Early phase clinical trials of sifalimumab have also been completed in other IMIDs. In dermatomyositis/polymyositis, sifalimumab produced a significant but modest (53%–66%) suppression of a 13-gene IFN signature which positively correlated with clinical improvement in muscle strength.[47] However, in a phase I study in psoriasis, sifalimumab failed to suppress the IFN gene signature and had no clinical activity.[47]

Rontalizumab, a human mAb against all 12 IFN-α subtypes, has been trialled in SLE but failed to reach its primary end point.[48] Interestingly, a trend towards efficacy was noted in IFN-low but not in IFN-high patients, and rontalizumab was not associated with increased viral infections.[48] These observations may suggest relatively inefficient target engagement, although differences in study design, particularly around management of concomitant immunosuppression, make a direct comparison with sifalimumab difficult. Differences in IFN-α subtype blockade between sifalimumab and rontalizumab may also have influenced their relative efficacy.

Induction of active immunity against IFN-α in a vaccine-based approach is also in clinical development. IFN-α kinoid (IFN-K) is a conjugate protein of inactivated IFN-α coupled to keyhole limpet haemocyanin.[49] In a placebo-controlled randomised dose-escalation study of 28 patients with mild-to-moderate SLE, 3 to 4 doses of IFN-K induced anti-INF-α antibodies.[49] Interestingly, anti-IFN-α antibody titres were higher in patients with a positive baseline IFN gene signature and correlated negatively with IFN gene expression at day 112.[49] The safety of such an approach must await further trials.

In contrast to neutralising IFN-α, it is also possible to block its receptor. Anifrolumab is a human mAb against subunit 1 of the IFN-α receptor (IFNAR) which, in a recent phase IIb clinical trial of 305 patients with SLE, showed efficacy versus placebo both for global and organ-specific disease activity.[50] Anifrolumab was also more effective in IFN-high patients and carried a

comparable dose-dependent risk of herpes zoster infection to that of sifalimumab.[50] In an indirect comparison, anifrolumab appeared to exert a more potent and sustained suppression of IFN gene expression compared with sifalimumab in two Japanese SLE cohorts.[51] Anifrolumab is also in phase I development for the treatment of systemic sclerosis.[52 53]

Upstream inhibition of the IFN-I axis

Several strategies for the upstream inhibition of IFN-I production are currently in early stages of development. BIIB059 is a humanised mAb against BDAC-2, a pDC-specific surface receptor that mediates a reduction in IFN-I production.[54] Data from a phase Ib trial in 12 patients with SLE demonstrated a reduction in IFN gene expression and improvement in skin lesions.[55] Talacotuzumab is a cytotoxic mAb against CD123, which is expressed in high levels on pDCs.[56] Talacotuzumab depleted pDCs from the blood of SLE patients in vitro, leading to inhibition of IFN-I gene expression.[56] In addition to antibody-based therapies, a number of small molecular inhibitors of TLR-7/8/9 signalling are currently in development for the treatment of SLE and psoriasis, although results of early phase clinical trials are yet to be formally published.[44]

Inhibition of type II IFNs

Although type I IFNs are the principal inducers of the IFN gene signature, type II and III IFNs also upregulate these genes.[44] IFN-γ signals via a different receptor (IFNGR) than IFN-I, although there is some overlap in downstream signalling cascades[40] (figure 2). An mAb against IFN-γ, AMG 811, is in development and has shown dose-dependent reductions in circulating levels of the IFN-γ-dependent protein CXCL10[57] and IFN-γ-modulated gene expression in whole blood from patients with SLE.[58] Furthermore, treatment with AMG 811 reduced both of these biomarkers in patients with active lupus nephritis in a small (n=28) phase I study, although transiently and with no discernible clinical effect.[59] There are currently few data surrounding the role of IFN-λ in autoimmunity, although evidence of a pathogenic role in SLE is emerging.[44]

Summary: targeting the IFN axis in SLE—what have we learnt?

SLE is a notoriously difficult disease in which to develop novel therapeutics, with many failures and just a single success (belimumab) in the biologic era. While encouraging, the data from targeting of the IFN axis remain early phase and, in part, contradictory. Nonetheless, the biology appears compelling and a multitude of agents are in development. Furthermore, the regulatory approval of Janus knase (JAK) inhibitors provides a further route to directly target IFN signalling, with agents whose pharmacokinetic and pharmacodynamic characteristics are well studied. With this broad armamentarium, and careful trial design, we can look forward to the hypothesis linking IFN activity and SLE to be definitively answered.

TARGETING CELL ADHESION

Integrin blockade

Adhesion molecules play a crucial role in the cell-cell interactions that are necessary for recruitment of circulating immune cells from the vasculature to local tissue sites. Especially important in this regard is the integrin family, which mediates strong adhesion between leucocytes and endothelial and mucosal epithelial cells by binding to extracellular matrix components and specific receptor molecules. Six integrins are expressed only on leucocytes: LFA-1 (αLβ2), Mac-1 (αMβ2), αxβ2, αdβ2, α4β7 and αEβ7.[60] Especially notable are: LFA-1, which plays a key role in the formation of the immunological synapse; α4β7, which mediates gut-specific lymphocyte homing via binding to MAdCAM-1 on the surface of gastrointestinal endothelial cells; and αEβ7, which binds E-cadherin on gut epithelial cells and may be important for lymphocyte retention within the mucosa.[60] Inhibition of lymphocyte recruitment to end organs can thus be achieved by blocking these interactions, with a specificity determined by the cellular tropism of the target cellular adhesion molecule (figure 3).

One of the first integrin blockers used in the treatment of autoimmunity was natalizumab, an mAb against the α4 integrin subunit. Natalizumab exerts a relatively non-specific blockade of lymphocyte recruitment at both the blood-brain barrier (α4β1 integrin) and the gut (α4β7 integrin) and is effective in the treatment of multiple sclerosis (MS)[61] and CD.[62] However, postmarketing surveillance of patients taking natalizumab demonstrated the development of progressive multifocal leukoencephalopathy (PML), a severe and often fatal central nervous system (CNS) infection caused by the JC virus.[63] Thus, while natalizumab continues to be used for the treatment of MS, its unfavourable risk:benefit profile limits its use in CD. Although licensed in the USA, it failed to gain regulatory approval for CD in Europe.[64] Similarly efalizumab, an mAb against the αL integrin subunit of LFA-1 and effective in the treatment of psoriasis, was withdrawn from the market in 2009 following case reports of PML.[65] Nevertheless, topical ocular use of lifitegrast, a small molecule inhibitor of LFA-1, has recently been licensed for the treatment of keratoconjunctivitis sicca.[66] Furthermore, two small molecule inhibitors of α4 integrin, carotegrast methyl[67] and firategrast,[68] are in development for the treatment of ulcerative colitis (UC) and MS, respectively.

In an attempt to reduce the risk of opportunistic infection, more specific integrin inhibitors have been developed. In particular, several mAbs have been developed against the gut-specific α4β7 integrin or its ligand, MAdCAM-1 (see online supplementary Table S2). Furthermore, etrolizumab, an mAb directed solely against the β7 integrin subunit, additionally inhibits binding of αEβ7 to E-cadherin. Whether this translates to superior clinical efficacy is yet to be determined. However, in a phase II study in moderate-to-severe UC, the efficacy of etrolizumab positively correlated with expression of αE in the intestinal mucosa, thereby providing a potential stratification marker for its use.[69] To date, these 'gut-specific' integrin inhibitors do not appear to be associated with an increased risk of PML.[70]

Aside from the (brief) use of efalizumab in psoriasis, integrin blockade has so far been of limited clinical utility outside of the setting of CNS and gut autoimmunity. A post hoc analysis of a randomised controlled trial (RCT) of vedolizumab in CD suggested a trend towards resolution of extraintestinal manifestations,[71] which was mirrored by preliminary data from a separate cohort of patients with UC and CD.[72] However, a case series of new-onset or exacerbated arthritis and sacroiliitis in patients treated with vedolizumab has recently been reported.[73] Alongside a bell-shaped dose-response in the UC trial of etrolizumab, these observations may suggest that both pro-inflammatory and anti-inflammatory lymphocyte subsets are targeted by integrin blockade.

Sphingosine-1-phosphate receptor blockade

The sphingosine-1-phosphate (S1P) receptor family comprises five members with effects on cell proliferation; migration

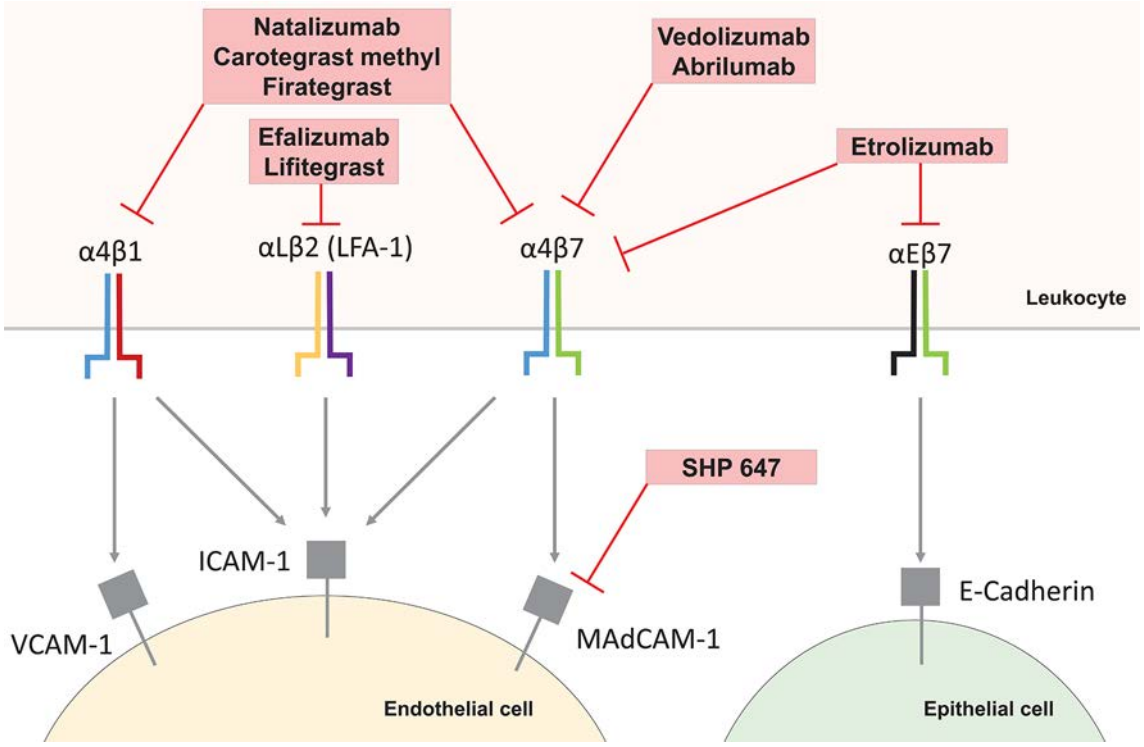


Figure 3 Overview of drugs targeted against integrin molecules and their ligands. ICAM-1, intercellular adhesion molecule 1; MAdCAM-1, mucosal vascular addressin cell adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1. Adapted from Bravatà *et al*.[70]

and survival; intercellular communication; vascular tone and endothelial barrier function.[74] In particular, S1P1 receptor has a key role in the trafficking of lymphocytes out of secondary lymphoid organs. Receptor agonists, via receptor internalisation and degradation, prevent B-cell and T-cell egress into the circulation. Fingolimod, a relatively non-specific small molecule S1P-receptor agonist, is approved for use in relapsing-remitting MS but has been associated with severe herpetic infections, as well as cardiac and hepatic adverse effects.[75] Recently , ozanimod, another small molecule agonist but more selective for S1P1 and S1P5 receptors, demonstrated efficacy in a phase II trial in moderate-to-severe UC, with a dose-related reduction in circulating lymphocytes and an acceptable safety profile.[76]

Summary: targeting cell adhesion — what have we learnt?

Targeting the molecules that underpin immune cell trafficking can have profound effects, both in terms of efficacy but also safety. In particular, the emergence of PML with natalizumab, and perhaps herpetic infection with fingolimod, may indicate a key role in microbiological latency. Nonetheless, an effective and safe therapy may emerge when it is possible to specifically target molecules on key effector subsets, such as the integrins expressed by gut-homing lymphocytes. While long-term safety data are awaited, mucosal αE expression may facilitate the targeting of etrolizumab to patients most likely to benefit from its use.

JANUS KINASE INHIBITION

JAKs are intracellular tyrosine kinases that play a crucial role in the signalling pathways of many cytokines involved in immunity and haematopoiesis. On receptor-cytokine binding and receptor dimerisation, receptor-associated JAKs cross-phosphorylate one another. Further phosphorylation of receptor-associated tyrosine residues provides docking sites for STAT proteins, which are also phosphorylated by JAKs.[77] Phosphorylated STAT molecules then dimerise and translocate to the nucleus, where they act as potent regulators of gene expression. There are four JAKs—JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2)—which function as heterodimers or, in the case of JAK2, also as a homodimer.[77] Different JAK dimers associate with different receptors, such that each JAK mediates signalling from a distinct, although overlapping, profile of cytokines (figure 4). Inhibition of JAK signalling therefore offers a novel mechanism by which to block a range of cytokines using a small-molecule drug.

First-generation JAK inhibitors

Tofacitinib is a pan-JAK inhibitor capable of inhibiting JAK3/1/2 and, to a lesser extent, TYK2.[78] Tofacitinib is licensed for its beneficial effects in RA,[79] and is currently in development for a range of other IMIDs including juvenile idiopathic arthritis, psoriasis, PsA and UC. Baricitinib and ruxolitinib are JAK1/2 inhibitors which, owing to the heterodimeric functionality of JAKs, exert a very similar spectrum of cytokine blockade to that of tofacitinib and have been trialled in a range of autoimmune diseases (table 2). Ruxolitinib is also licensed for the treatment of myelodysplasia, although the suppressive effects of first-generation JAK inhibitors on haematopoiesis are an unwanted adverse effect in the context of IMIDs. This can be circumvented by topical formulations for dermatological indications,[80] although may be an issue for pan-JAK inhibitors when systemic treatment is required.

Second-generation JAK inhibitors

Recent years have seen the development of a 'second generation' of JAK inhibitors for the treatment of IMIDs that exert a selective blockade of JAK1 or JAK3 which, in theory, should have less risk of haematopoietic toxicity—an effect largely secondary to JAK2 inhibition (figure 4).[77] However, neutropaenia and lymphopoenia are still encountered in some trials of these agents

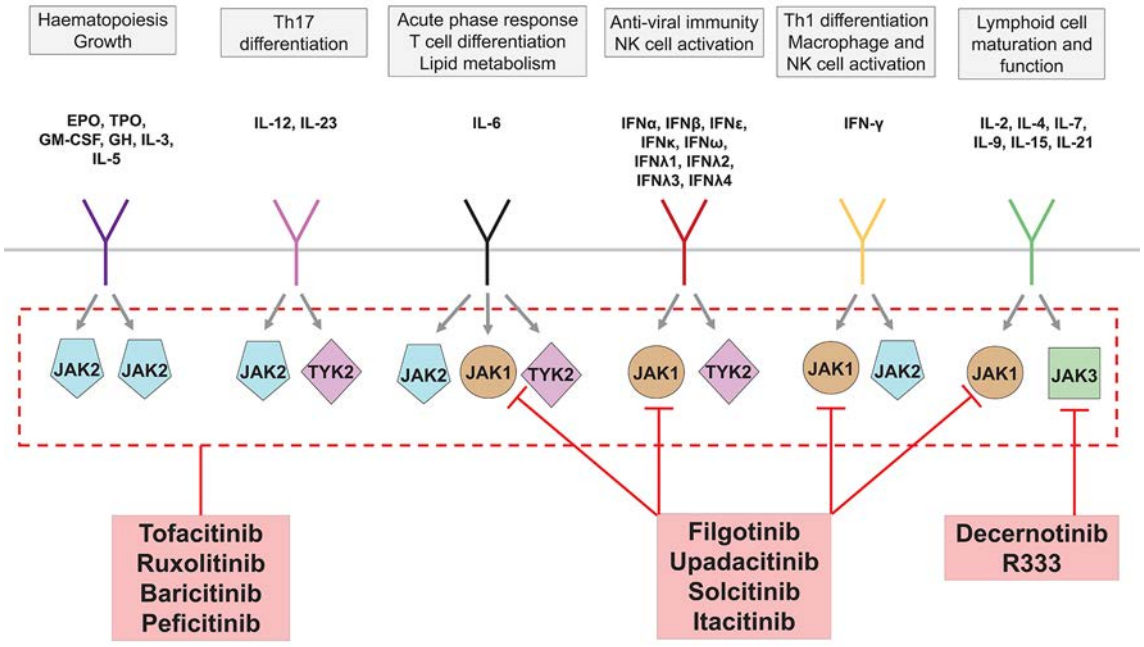


Figure 4 Overview of Janus kinase (JAK) inhibitors developed for the treatment of immune-mediated inflammatory diseases. JAK2-specific inhibitors have been developed for the treatment of haematological malignancy, although are omitted here for simplicity. EPO, erythropoietin; GH, growth hormone; IFN, interferon; GM-CSF, granulocyte macrophage colony-stimulating factor; TPO, thrombopoietin; Tyk2, tyrosine kinase 2. Adapted from reference.[77]

suggesting either non-redundant JAK1/JAK3/TYK2-dependent haematopoietic mechanisms or, more likely, suboptimal selectivity.[81] Indeed, as with most small molecules drugs, target selectivity of JAK inhibitors depends both on the assay used and the concentration/dose studied in vitro or in vivo.[81] Combined with further recognised adverse effects including transaminitis, dyslipidaemia, herpes zoster reactivation and lymphopoenia,[82] these drugs have a modestly distinct adverse event profile to biologic drugs. Thus, while oral dosing and a rapid onset of efficacy may prove attractive to both practitioners and patients, regulatory approval has not proved straightforward for either tofacitinib[83] or baricitinib.[84] Furthermore, the focus on JAK1-specific and JAK3-specific inhibition neglects IL-12/IL-23 signalling, which relies on JAK2/TYK2 heterodimers. It is thus unsurprising that JAK1 and JAK3 selective inhibitors have so far proved disappointing in the treatment of psoriasis,[85] PsA and AS (table 2). Selective inhibition of TYK2 should have theoretically greater efficacy for these diseases, and several such inhibitors are in early preclinical development.[86]

Summary: JAK inhibition — what have we learnt?

The development of JAK inhibitors has brought a new approach to the treatment of IMIDs, and rapid onset of biologic-like potency in an oral formulation will prove attractive for diseases such as RA. Furthermore, JAK inhibition has helped to validate aspects of immune physiology, such as the role of γ-chain cytokines in lymphopoiesis. However, JAK inhibitors are of necessity less selective than their biologic counterparts, blocking signalling across multiple cytokine axes simultaneously. Furthermore, as with any small molecule drug, target specificity is not absolute and will depend on the dose delivered to tissues. Consequently, efficacy and toxicity in the clinic may differ from that predicted from in vitro testing, and even from clinical trials. Long-term safety data are therefore required, combined with head-to-head studies, to determine the optimal positioning of JAK inhibitors alongside biologic agents.

TARGETING SPECIFIC CELLULAR SUBSETS

Therapeutic immune modulation can also be achieved via selective depletion, expansion or blockade of specific immune cell subsets. Early examples of this approach include the cell-depleting monoclonal antibodies alemtuzumab (anti-CD52) and rituximab (anti-CD20), which are now licensed for the treatment of MS and RA, respectively. Recent years have seen further development of novel therapies against B-cells as well as agents to expand Tregs, with both therapeutic approaches being trialled in the treatment of IMIDs.

Therapies targeting B cells

Following in the footsteps of rituximab, several other B-cell-depleting mAbs have been developed (see online supplementary Table S3). Ocrelizumab is a humanised anti-CD20 mAb that is effective in the treatment of both relapsing-remitting[87] and primary-progressive[88] MS. To date, it is the only therapy to demonstrate efficacy in primary progressive MS; rituximab, in comparison, has only proven effective in relapsing-remitting disease.[89] It remains to be determined whether this reflects differences in study design, drug posology or a true biological difference between rituximab and ocrelizumab. Nevertheless, development of ocrelizumab in other IMIDs, including RA and SLE, was terminated due to an adverse safety profile, suggesting the possibility of a true difference in the biological function of these two agents despite their common molecular target. Obinutuzumab is an anti-CD20 mAb whose cytotoxic properties have been refined by glycoengineering. B-cell depletion by this

Table 2 Development of drugs for IMIDs that target Janus kinases (JAKs). Development status based on http://adisinsight.springer.com, accessed 30 May 2017. AS, ankylosing spondylitis; CD, Crohn's disease; IMID, immune-mediated inflammatory diseases; JIA, juvenile idiopathic arthritis; P-I, phase I clinical trial; P-II, phase II clinical trial; P-III, phase III clinical trial; SLE, systemic lupus erythematosus; Syk, spleen tyrosine kinase; TYK2, tyrosine kinase 2; UC, ulcerative colitis. *Baricitinib approved by the European Medicines Agency, although rejected by the Food and Drug Administration (April 2017).

Drug	JAK targets	Developer	Psoriasis	PsA	AS	RA	IBD	Other indications
First-generation pan-JAK inhibitors								
Tofacitinib [CP-690550, tasocitinib] (*Xeljanz*, *Jaquinus*)	JAK1, JAK2, JAK3, (TYK2)	Pfizer	P-III (oral and topical)	Submitted	Discontinued	Marketed	P-III (UC)	JIA (P-III) Atopic dermatitis (P-II) Dermatomyositis (P-I) SLE (P-I)
Ruxolitinib [INC-424, INCB-18424] (*Jakafi*, *Jakavi*)	JAK1, JAK2	Novartis, Incyte	P-II (topical)			Discontinued		Polycythaemia rubra vera (marketed) Myelofibrosis (marketed) Graft-versus-host disease (P-III) Various other myeloproliferative disorders (P-II/P-III) Vitiligo (topical, P-II) Alopecia areata (topical and oral, P-II)
Baricitinib [INCB-28050, LY-3009104] (*Olumiant*)	JAK1, JAK2	Eli Lilly, Incyte	Discontinued	P-III		Marketed*		SLE (P-II) Atopic dermatitis (P-II)
Peficitinib [ASP-015K, JNJ-54781532]	JAK1, JAK2, JAK3, TYK2	Astellas Pharma	Discontinued			P-III	Discontinued (UC)	
Second-generation selective JAK inhibitors								
Filgotinib [G-146034, GLPG-0634, GS-6034]	JAK1	Galapagos NV, Gilead Sciences		P-II	P-II	P-III	P-III (UC and CD)	Sjogren's syndrome (P-II) Cutaneous lupus (P-II)
Upadacitinib [ABT494]	JAK1	AbbVie		P-III		P-III	P-III (UC) P-II (CD)	Atopic dermatitis (P-II)
Solcitinib [G154578, GLPG-0778, GSK-2586184]	JAK1	GlaxoSmithKline	Discontinued				Discontinued (UC)	SLE (discontinued)
Itacitinib [INCB-039110]	JAK1	AstraZeneca, Incyte	Discontinued			Discontinued		Graft-versus-host disease (P-II) Hodgkin's lymphoma (P-II) Non-small cell lung cancer (P-II)
Decernotinib [Adelatinib, VRT-831509, VX-509]	JAK3	Vertex Pharmaceuticals				Discontinued		
R333	JAK3, Syk	Rigel Pharmaceuticals						Cutaneous lupus (discontinued)

afucosylated mAb takes advantage of modified FcγR interactions as well as reduced redistribution and modulation of CD20.[90] It is marketed for certain haematological malignancies and is in phase II trials for SLE (NCT02550652).

In addition to cellular depletion, recent years have witnessed the development of several strategies to inhibit B-cell differentiation and survival. B-cell activating factor (BAFF) and APRIL (a proliferation-inducing ligand) are B-cell stimulating molecules important in B-cell maturation and plasma cell survival/class-switching, respectively.[91] Attempts to inhibit BAFF and APRIL have, to date, yielded mixed responses. Belimumab, an mAb against soluble BAFF, is marketed for the treatment of SLE, although there is little evidence to support efficacy outside of joint and skin involvement.[92] Tabalumab—an mAb against both soluble and membrane-bound BAFF—and the anti-BAFF peptibody blisibimod both exhibited disappointing efficacy for SLE in recent phase III clinical trials.[93–95] Both BAFF and APRIL bind to transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI).[91] Atacicept and RCT 18 are TACI:IgG-Fc fusion peptides capable of blocking both APRIL and BAFF, and both are in development for SLE, although concerns remain surrounding their associated infection risk.[91] Perplexingly, BAFF/APRIL antagonism has limited efficacy in RA despite the success of rituximab in this setting. This may in part be explained by B-cell modulatory effects, such as APRIL-mediated IL-10 production by regulatory B cells,[96] and the relative functional importance of such mechanisms in different disease settings.

Therapies targeting Treg cells

In contrast to depletion and downregulation of B-cell populations, alternative strategies have been used to stimulate Treg populations to abrogate autoimmunity. One area that has gained recent attention is the use of low-dose recombinant IL-2. Whereas high doses of IL-2 stimulate effector T cells are used in the treatment of certain forms of cancer such as malignant melanoma, low doses preferentially expand Treg populations.[97] Indeed, low-dose IL-2 therapy has shown promise in early phase clinical trials in a range of IMIDs including hepatitis C virus-induced vasculitis,[98] graft-versus-host disease,[99] SLE,[100] type I diabetes mellitus[101] and alopecia areata.[102] Several strategies to boost the tolerogenic effect of low dose IL-2 have been proposed, including the design of 'second-generation' IL-2 molecules with longer half-life and improved target cellular profiles, the combination of low-dose IL-2 with existing biological agents and even combination with vaccines to promote antigen-specific tolerance.[97]

Various alternative approaches to stimulate Tregs using mAbs are in development. TGN-1412 is a super-agonist mAb against the costimulatory molecule CD28. In a notorious phase I study of healthy volunteers in 2006, it caused a life-threatening cytokine storm. This was attributed to CD28-mediated activation of tissue-resident memory T cells—an effect not observed in preclinical cynomolgus macaque studies, in which CD28 is downregulated on these cells.[103] Nevertheless, when used at a much lower dose, TGN-1412 can specifically activate Tregs and development has now been relaunched under the name theraliximab.[104] Tregalizumab is an mAb against CD4 and, in contrast to other CD4 mAbs, binds to a distant epitope and has been shown to specifically activate Tregs in preclinical studies.[105] Nevertheless, a phase IIb study in RA failed to show improvement in ACR20 response compared with placebo,[105] and further development of the drug for this indication has been discontinued.

Recent years have seen growing interest in so-called Treg epitopes (Tregitopes)—highly conserved amino acid sequences within IgG molecules which can be presented on a wide range of major histocompatibility complex-II alleles to selectively activate Tregs.[106] It has been proposed that Tregitopes represent an evolutionary mechanism by which to suppress autoreactivity to the wide array of different immunoglobulin molecules that are created during immune development,[107] and may be the mechanism underlying the efficacy of intravenous immunoglobulin in the treatment of IMIDs.[108] Tregitopes can ameliorate inflammation in several murine models of autoimmunity, and are in preclinical stages of development for the treatment of IMIDs.[107]

Several cellular therapeutic approaches to enhance Treg function are also in the early stages of development for the treatment of IMIDs, including exogenous Treg transfer[109] and tolerogenic dendritic cell therapies.[110 111]

Summary: targeting specific cellular subsets — what have we learnt?

Recent years have witnessed a rapid expansion in the array of biologic therapies to selectively deplete or inhibit B-cells, and the emergence of therapeutic strategies aimed at expanding Tregs. Novel aspects include glycoengineering to optimise depleting potency, where required. However, despite apparent success in preclinical development, efficacy in later stage clinical trials has been somewhat mixed. For B-cell targeted therapy this may reflect the various B-cell subsets and their heterogeneous function(s). Thus, more focused therapy may be required to optimise efficacy. Posology of these agents is also clearly of importance, as demonstrated by the widely contrasting effects of low -dose and high-dose IL-2 and TGN-1412 therapies. In terms of cellular therapies , the long-term stability of therapeutically expanded Tregs and the risk of conversion to an effector phenotype remains uncertain.[112] Furthermore, antigen-specific approaches are likely to provide the optimal route for cell-targeted therapies.

NEWER TECHNOLOGIES

Bispecific antibodies

Despite the potent blockade of cytokine signalling afforded by biologic therapies, many patients have only a partial or transient response. In some cases, this is attributable to immunogenicity against the biologic agent, although in other cases likely reflects redundancy and/or plasticity in the underlying autoimmune processes. Attempts to block multiple cytokines through the simultaneous use of different biologics have, however, been limited by unacceptable adverse effects without superior efficacy.[113–115]

With advances in mAb technology, a number of approaches enable the targeting of multiple molecular species by a single therapeutic.[116] For example, ABT-122 is a so-called dual variable domain mAb against both IL-17 and TNF-α. In small, early phase studies it appears to have a similar safety profile to adalimumab in PsA and RA.[117] Furthermore, in a phase II trial in patients with PsA with an inadequate response to methotrexate, there was some evidence of superiority of ABT-122 when compared with adalimumab for both ACR70 (ABT-122 vs ADA, 31.5% vs 15.3%, $p<0.05$) and PASI75 (77.6% vs 57.6%, $p<0.05$) responses.[118] In contrast, a phase Ib/IIa trial in psoriasis of COVA322, a so-called fynomab that targets both IL-17 and TNF-α, was terminated due to safety concerns (NCT02243787, results not published).

The original trials combining two biologic drugs can be criticised for not studying sufficiently low doses of these potentially

synergistic combinations. A disadvantage of bispecific and trispecific reagents, however, is that they only allow fixed ratios of cytokine blockade to be tested.

Gene therapy approaches

Mongersen is a modified release antisense nucleotide to mothers against decapentaplegic homolog 7 (SMAD-7), designed to be released into the terminal ileum and proximal colon.[119] SMAD-7 is central to transforming growth factor-β1 signalling, itself important in the pathogenesis of CD.[120] In a phase II trial, a short course of mongersen proved superior to placebo at inducing remission in patients with active CD.[121] Most adverse events were attributable to the disease itself, and this trial provides proof of principle that it is possible to interfere with immunopathological processes at the level of gene transcription, by local delivery of a nucleotide-based therapy.

Summary — what have we learnt from newer technologies?

It is early days but the first trials of bispecific antibodies have provided mixed results. A raft of agents are in development, including trivalent nanobodies and PEGylated single chain fragment variables.[122] Not all of these drugs will reach the clinic, certainly in IMIDs. Furthermore, in some cases, the anticipated advantages of poly-targeting could be offset by lack of effector function and short half-lives, but careful choice of disease and trial design should mitigate against these potential shortcomings. In terms of gene therapy, it is again early days but there is clearly the potential for local delivery of such agents in articular diseases, as in CD.

CONCLUSIONS

The future remains exciting for clinicians treating IMIDs, and for their patients. Targeted therapies, as well as providing new treatment paradigms, continue to inform us about the pathogenesis of disease and its complications. In this brief review, we have highlighted just a few examples of novel approaches, particularly where data have provided new downstream knowledge and teachings. However, many challenges remain—in particular, the ability to target these various approaches to both the diseases and the patients who are most likely to benefit. Equally challenging is the need for head-to-head comparisons between different agents, to reliably dissect the relative contributions of distinct pathways to a particular disease. Future trials will need to become increasingly sophisticated in order to address these varying requirements.

Contributors Conception: JDI. Design, analysis, drafting and final approval of the manuscript: JDI, KFB.

Funding KFB is supported by a Wellcome Trust Fellowship in Translational Medicine and Therapeutics (102595/Z/13/A) and a grant from the National Institute for Health Research Newcastle Biomedical Research Centre (BH136167/PD0045) based at Newcastle Hospitals NHS Foundation Trust and Newcastle University. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests JDI has received honoraria, research grants or consulting fees from AbbVie; Biogen; Bristol-Myers-Squibb Company; Celltrion Healthcare; Chugai Pharmaceutical; Eli Lilly and Company; Hospira; Janssen Pharmaceuticals; Merck Serono S A; Pfizer; and Roche Laboratories. KFB has no competing interests to declare.

Provenance and peer review Commissioned; externally peer reviewed.

Data sharing statement None declared.

REFERENCES

1 Roach DR, Bean AG, Demangel C, *et al*. TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. *J Immunol* 2002;168:4620–7.
2 Gizinski AM, Fox DA. T cell subsets and their role in the pathogenesis of rheumatic disease. *Curr Opin Rheumatol* 2014;26:204–10.
3 Patel DD, Kuchroo VK. Th17 cell pathway in human immunity: lessons from Genetics and therapeutic interventions. *Immunity* 2015;43:1040–51.
4 Kim BS, Park YJ, Chung Y. Targeting IL-17 in autoimmunity and inflammation. *Arch Pharm Res* 2016;39:1537–47.
5 Bartlett HS, Million RP. Targeting the IL-17-T(H)17 pathway. *Nat Rev Drug Discov* 2015;14:11–12.
6 Beringer A, Noack M, Miossec P. IL-17 in chronic inflammation: from Discovery to targeting. *Trends Mol Med* 2016;22:230–41.
7 Patel DD, Lee DM, Kolbinger F, *et al*. Effect of IL-17A blockade with secukinumab in autoimmune diseases. *Ann Rheum Dis* 2013;72 Suppl 2(Suppl 2):iii116–iii123.
8 Koenders MI, van den Berg WB. Secukinumab for rheumatology: development and its potential place in therapy. *Drug Des Devel Ther* 2016;10:2069–80.
9 Griffiths CE, Reich K, Lebwohl M, *et al*. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet* 2015;386:541–51.
10 Mease PJ, van der Heijde D, Ritchlin CT, *et al*. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis* 2017;76:79–87.
11 Glatt S, Helmer E, Haier B, *et al*. First-in-human randomised study of bimekizumab, a humanised monoclonal antibody and selective dual inhibitor of IL-17A and IL-17 F, in mild psoriasis. *Br J Clin Pharmacol* (Epub ahead of print: 13 Nov 2016).
12 Glatt S, Strimenopoulou F, Vajjah P, *et al*. OP0108 Bimekizumab, A Monoclonal Antibody That Inhibits both IL-17A and IL-17F, Produces A Profound Response in both Skin and Joints: Results of An Early-Phase, Proof-of-Concept Study in Psoriatic Arthritis:. *Ann Rheum Dis* 2016;75(Suppl 2):95.3–6.
13 Nirula A, Nilsen J, Klekotka P, *et al*. Effect of IL-17 receptor A blockade with brodalumab in inflammatory diseases. *Rheumatology* 2016;55:ii43–ii55. (Oxford).
14 Kleinschek MA, Owyang AM, Joyce-Shaikh B, *et al*. IL-25 regulates Th17 function in autoimmune inflammation. *J Exp Med* 2007;204:161–70.
15 Su J, Chen T, Ji XY, Xy J, *et al*. IL-25 downregulates Th1/Th17 immune response in an IL-10-dependent manner in inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19:720–8.
16 Liu D, Cao T, Wang N, *et al*. IL-25 attenuates rheumatoid arthritis through suppression of Th17 immune responses in an IL-13-dependent manner. *Sci Rep* 2016;6:36002.
17 Pavelka K, Chon Y, Newmark R, *et al*. A study to evaluate the safety, tolerability, and efficacy of brodalumab in subjects with rheumatoid arthritis and an inadequate response to methotrexate. *J Rheumatol* 2015;42:912–9.
18 Genovese MC, Durez P, Richards HB, *et al*. Efficacy and safety of secukinumab in patients with rheumatoid arthritis: a phase II, dose-finding, double-blind, randomised, placebo controlled study. *Ann Rheum Dis* 2013;72:863–9.
19 Genovese MC, Greenwald M, Cho CS, *et al*. A phase II randomized study of subcutaneous ixekizumab, an anti-interleukin-17 monoclonal antibody, in rheumatoid arthritis patients who were naive to biologic agents or had an inadequate response to tumor necrosis factor inhibitors. *Arthritis Rheumatol* 2014;66:1693–704.
20 Hueber W, Sands BE, Lewitzky S, *et al*. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. *Gut* 2012;61:1693–700.
21 Targan SR, Feagan B, Vermeire S, *et al*. A Randomized, Double-Blind, Placebo-Controlled phase 2 study of Brodalumab in Patients with Moderate-to-Severe crohn's Disease. *Am J Gastroenterol* 2016;111:1599–607.
22 Colombel JF, Sendid B, Jouault T, *et al*. Secukinumab failure in Crohn's disease: the yeast connection? *Gut* 2013;62:800.2–1.
23 O'Connor W, Kamanaka M, Booth CJ, *et al*. A protective function for interleukin 17A in T cell-mediated intestinal inflammation. *Nat Immunol* 2009;10:603–9.
24 McInnes IB, Mease PJ, Kirkham B, *et al*. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015;386:1137–46.
25 Schmidt C. Suicidal thoughts end Amgen's blockbuster aspirations for psoriasis drug. *Nat Biotechnol* 2015;33:894–5.
26 Chiricozzi A, Romanelli M, Saraceno R, *et al*. No meaningful association between suicidal behavior and the use of IL-17A-neutralizing or IL-17RA-blocking agents. *Expert Opin Drug Saf* 2016;15:1653–9.
27 Croxford AL, Kulig P, Becher B. IL-12-and IL-23 in health and disease. *Cytokine Growth Factor Rev* 2014;25:415–21.
28 Teng MW, Bowman EP, McElwee JJ, *et al*. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. *Nat Med* 2015;21:719–29.

29 Johnsson HJ, McInnes IB. Interleukin-12 and interleukin-23 inhibition in psoriatic arthritis. *Clin Exp Rheumatol* 2015;33(5 Suppl 93):S115–8.
30 Poddubnyy D, Hermann KG, Callhoff J, *et al*. Ustekinumab for the treatment of patients with active ankylosing spondylitis: results of a 28-week, prospective, open-label, proof-of-concept study (TOPAS). *Ann Rheum Dis* 2014;73:817–23.
31 Kavanaugh A, Puig L, Gottlieb AB, *et al*. Efficacy and safety of ustekinumab in psoriatic arthritis patients with peripheral arthritis and physician-reported spondylitis: post-hoc analyses from two phase III, Multicentre, double-blind, placebo-controlled studies (PSUMMIT-1/PSUMMIT-2). *Ann Rheum Dis* 2016;75:1984–8.
32 MacDonald JK, Nguyen TM, Khanna R, *et al*. Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2016;11:Cd007572.
33 Feagan BG, Sandborn WJ, Gasink C, *et al*. Ustekinumab as induction and maintenance therapy for crohn's Disease. *N Engl J Med* 2016;375:1946–60.
34 Blauvelt A, Reich K, Tsai TF, *et al*. Secukinumab is superior to Ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study. *J Am Acad Dermatol* 2017;76:60–9.
35 Köck K, Pan WJ, Gow JM, *et al*. Preclinical development of AMG 139, a human antibody specifically targeting IL-23. *Br J Pharmacol* 2015;172:159–72.
36 Blauvelt A, Papp KA, Griffiths CE, *et al*. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol* 2017;76:405–17.
37 Lebwohl M, Strober B, Menter A, *et al*. Phase 3 studies comparing brodalumab with Ustekinumab in Psoriasis. *N Engl J Med* 2015;373:1318–28.
38 Papp KA, Blauvelt A, Bukhalo M, *et al*. Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis. *N Engl J Med* 2017;376:1551–60.
39 Zhang YZ, Li YY, Yy L. Inflammatory bowel disease: pathogenesis. *World J Gastroenterol* 2014;20:91–9.
40 Schneider WM, Chevillotte MD, Rice CM. Interferon-stimulated genes: a complex web of host defenses. *Annu Rev Immunol* 2014;32:513–45.
41 Ronnblom L. The importance of the type I interferon system in autoimmunity. *Clin Exp Rheumatol* 2016;4(Suppl 98):21–4.
42 Swiecki M, Colonna M. The multifaceted biology of plasmacytoid dendritic cells. *Nat Rev Immunol* 2015;15:471–85.
43 Wilson LE, Widman D, Dikman SH, *et al*. Autoimmune disease complicating antiviral therapy for hepatitis C virus infection. *Semin Arthritis Rheum* 2002;32:163–73.
44 Oon S, Wilson NJ, Wicks I. Targeted therapeutics in SLE: emerging strategies to modulate the interferon pathway. *Clin Transl Immunology* 2016;5:e79.
45 Mathian A, Hie M, Cohen-Aubart F, *et al*. Targeting interferons in systemic lupus erythematosus: current and future prospects. *Drugs* 2015;75:835–46.
46 Khamashta M, Merrill JT, Werth VP, *et al*. Sifalimumab, an anti-interferon-α monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* 2016;75:1909–16.
47 Tcherepanova I, Curtis M, Sale M, *et al*. SAT0193 Results of a randomized placebo controlled phase ia study of AGS-009, a humanized anti-interferon-α monoclonal antibody in subjects with systemic lupus erythematosus. *Ann Rheum Dis* 2013;71(Suppl 3):536.3–7.
48 Kalunian KC, Merrill JT, Maciuca R, *et al*. A phase II study of the efficacy and safety of rontalizumab (rhuMAb interferon-α) in patients with systemic lupus erythematosus (ROSE). *Ann Rheum Dis* 2016;75:196–202.
49 Lauwerys BR, Hachulla E, Spertini F, *et al*. Down-regulation of interferon signature in systemic lupus erythematosus patients by active immunization with interferon α-kinoid. *Arthritis Rheum* 2013;65:447–56.
50 Furie R, Khamashta M, Merrill JT, *et al*. Anifrolumab, an Anti-Interferon-α receptor monoclonal antibody, in Moderate-to-Severe systemic lupus erythematosus. *Arthritis Rheumatol* 2017;69:376–86.
51 Morehouse C, Chang L, Wang L, *et al*. Target modulation of a type I interferon (IFN) Gene signature with Sifalimumab or Anifrolumab in systemic lupus erythematosus (SLE) Patients in two Open label phase 2 japanese trials [abstract]. *Arthritis Rheumatol* 2014;66 http://acrabstracts.org/abstract/target-modulation-of-a-type-i-interferon-ifn-gene-signature-with-sifalimumab-or-anifrolumab-in-systemic-lupus-erythematosus-sle-patients-in-two-open-label-phase-2-japanese-trials/.
52 Guo X, Higgs BW, Bay-Jensen AC, *et al*. Suppression of T cell activation and Collagen Accumulation by an Anti-IFNAR1 mAb, Anifrolumab, in adult patients with systemic sclerosis. *J Invest Dermatol* 2015;135:2402–9.
53 Goldberg A, Geppert T, Schiopu E, *et al*. Dose-escalation of human anti-interferon-α receptor monoclonal antibody MEDI-546 in subjects with systemic sclerosis: a phase 1, multicenter, open label study. *Arthritis Res Ther* 2014;16:R57.
54 Pellerin A, Otero K, Czerkowicz JM, *et al*. Anti-BDCA2 monoclonal antibody inhibits plasmacytoid dendritic cell activation through Fc-dependent and Fc-independent mechanisms. *EMBO Mol Med* 2015;7:464–76.
55 Furie R, Werth VP, Merola J, *et al*. A monoclonal antibody targeting BDCA2, shows evidence of biological activity and early clinical proof of Concept in Subjects with active cutaneous SLE [abstract]. *Arthritis Rheumatol* 2016;68. BIIB059 http://acrabstracts.org/abstract/biib059-a-monoclonal-antibody-targeting-bdca2-shows-evidence-of-biological-activity-and-early-clinical-proof-of-concept-in-subjects-with-active-cutaneous-sle/.
56 Oon S, Huynh H, Tai TY, *et al*. A cytotoxic anti-IL-3Rα antibody targets key cells and cytokines implicated in systemic lupus erythematosus. *JCI Insight* 2016;1:e86131.
57 Chen P, Vu T, Narayanan A, *et al*. Pharmacokinetic and pharmacodynamic relationship of AMG 811, an anti-IFN-γ IgG1 monoclonal antibody, in patients with systemic lupus erythematosus. *Pharm Res* 2015;32:640–53.
58 Welcher AA, Boedigheimer M, Kivitz AJ, *et al*. Blockade of interferon-γ normalizes interferon-regulated gene expression and serum CXCL10 levels in patients with systemic lupus erythematosus. *Arthritis Rheumatol* 2015;67:2713–22.
59 Martin DA, Amoura Z, Romero-Diaz J, *et al*. THU0389 A Multiple Dose Study of AMG 811 (Anti-IFN-Gamma) in Subjects with Systemic Lupus Erythematosus and Active Nephritis. *Ann Rheum Dis* 2015;74(Suppl 2):337.2–337.
60 Ley K, Rivera-Nieves J, Sandborn WJ, *et al*. Integrin-based therapeutics: biological basis, clinical use and new drugs. *Nat Rev Drug Discov* 2016;15:173–83.
61 Pucci E, Giuliani G, Solari A, *et al*. Natalizumab for relapsing remitting multiple sclerosis. *Cochrane Database Syst Rev* 2011;10:Cd007621.
62 MacDonald JK, McDonald JW. Natalizumab for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007;1:Cd006097.
63 Bloomgren G, Richman S, Hotermans C, *et al*. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med* 2012;366:1870–80.
64 Agency EMLondon*Questions and answers on recommendation for the refusal of the marketing authorisation for natalizumab Elan Pharma*2007European Medicines Agencyhttp://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/000624/WC500070716.pdf (Accessed March 21, 2017).
65 Kothary N, Diak IL, Brinker A, *et al*. Progressive multifocal leukoencephalopathy associated with efalizumab use in psoriasis patients. *J Am Acad Dermatol* 2011;65:546–51.
66 Holland EJ, Luchs J, Karpecki PM, *et al*. Lifitegrast for the treatment of Dry Eye Disease: results of a phase III, Randomized, Double-Masked, Placebo-Controlled Trial (OPUS-3). *Ophthalmology* 2017;124:53–60.
67 Yoshimura N, Watanabe M, Motoya S, *et al*. Safety and efficacy of AJM300, an oral antagonist of α4 integrin, in induction therapy for patients with active ulcerative colitis. *Gastroenterology* 2015;149:1775–83.
68 Miller DH, Weber T, Grove R, *et al*. Firategrast for relapsing remitting multiple sclerosis: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2012;11:131–9.
69 Vermeire S, O'Byrne S, Keir M, *et al*. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. *Lancet* 2014;384:309–18.
70 Bravatà I, Allocca M, Fiorino G, *et al*. Integrins and adhesion molecules as targets to treat inflammatory bowel disease. *Curr Opin Pharmacol* 2015;25:67–71.
71 Rubin D, Feagan B, Dryden G, *et al*. The effect of Vedolizumab on Extraintestinal Manifestations in patients with Crohn's Disease in GEMINI 2 [abstract].. *Inflamm Bowel Dis* 2016(22):P-105 http://journals.lww.com/ibdjournal/Abstract/2016/03001/P_105_The_Effect_of_Vedolizumab_on_Extraintestinal.130.aspx (Accessed March 21, 2017).
72 Orlando A, Orlando R, Ciccia F, *et al*. Clinical benefit of vedolizumab on articular manifestations in patients with active spondyloarthritis associated with inflammatory bowel disease. *Ann Rheum Dis* 2017;76:e31.
73 Varkas G, Thevissen K, De Brabanter G, *et al*. An induction or flare of arthritis and/or sacroiliitis by vedolizumab in inflammatory bowel disease: a case series. *Ann Rheum Dis* 2017;76:878–81.
74 O'Sullivan S, Dev KK. Sphingosine-1-phosphate receptor therapies: advances in clinical trials for CNS-related diseases. *Neuropharmacology* 2017;113–597–607.
75 Cohen JA, Barkhof F, Comi G, *et al*. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010;362:402–15.
76 Sandborn WJ, Feagan BG, Wolf DC, *et al*. Ozanimod induction and Maintenance treatment for Ulcerative Colitis. *N Engl J Med* 2016;374:1754–62.
77 Banerjee S, Biehl A, Gadina M, *et al*. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. *Drugs* 2017;77:521–46.
78 Hodge JA, Kawabata TT, Krishnaswami S, *et al*. The mechanism of action of tofacitinib - an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2016;34:318–28.
79 van Vollenhoven RF, Fleischmann R, Cohen S, *et al*. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012;367:508–19.
80 Damsky W, King BA. JAK inhibitors in dermatology: the promise of a new drug class. *J Am Acad Dermatol* 2017;76:736–44.
81 Gadina M, Schwartz DM, O'Shea JJ. Decernotinib: a Next-Generation Jakinib. *Arthritis Rheumatol* 2016;68:31–4.
82 Nakayamada S, Kubo S, Iwata S, *et al*. Recent Progress in JAK inhibitors for the treatment of Rheumatoid Arthritis. *BioDrugs* 2016;30:407–19.
83 Agency EMXeljanz: EPAR - Public Assessment Report.London European Medicines Agency 2017 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004214/WC500224913.pdf (Accessed May 30, 2017).

84 Eli Lilly and Company and Incyte Corporation. U.S. FDA Issues Complete Response Letter for Baricitinib. Indianapolis: Business Wire 2017 http://www.businesswire.com/news/home/20170414005051/en/ (Accessed May 30, 2017).
85 Bachelez H, van de Kerkhof PC, Strohal R, *et al*. Tofacitinib versus Etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. *Lancet* 2015;386:552–61.
86 Yogo T, Nagamiya H, Seto M, *et al*. Structure-Based design and synthesis of 3-Amino-1,5-dihydro-4H-pyrazolopyridin-4-one derivatives as tyrosine kinase 2 inhibitors. *J Med Chem* 2016;59:733–49.
87 Hauser SL, Bar-Or A, Comi G, *et al*. Ocrelizumab versus interferon Beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2017;376:221–34.
88 Montalban X, Hauser SL, Kappos L, *et al*. Ocrelizumab versus Placebo in Primary Progressive Multiple sclerosis. *N Engl J Med* 2017;376:209–20.
89 Calabresi PA. B-Cell depletion - A Frontier in monoclonal antibodies for multiple sclerosis. *N Engl J Med* 2017;376:280–2.
90 Reddy V, Dahal LN, Cragg MS, *et al*. Optimising B-cell depletion in autoimmune disease: is obinutuzumab the answer? *Drug Discov Today* 2016;21:1330–8.
91 Samy E, Wax S, Huard B, *et al*. Targeting BAFF and APRIL in systemic lupus erythematosus and other antibody-associated diseases. *Int Rev Immunol* 2017;36:3–19.
92 Guerreiro Castro S, Isenberg DA. Belimumab in systemic lupus erythematosus (SLE): evidence-to-date and clinical usefulness. *Ther Adv Musculoskelet Dis* 2017;9:75–85.
93 Merrill JT, van Vollenhoven RF, Buyon JP, *et al*. Efficacy and safety of subcutaneous tabalumab, a monoclonal antibody to B-cell activating factor, in patients with systemic lupus erythematosus: results from ILLUMINATE-2, a 52-week, phase III, Multicentre, randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* 2016;75:332–40.
94 Isenberg DA, Petri M, Kalunian K, *et al*. Efficacy and safety of subcutaneous tabalumab in patients with systemic lupus erythematosus: results from ILLUMINATE-1, a 52-week, phase III, Multicentre, randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* 2016;75:323–31.
95 Pharmaceuticals A. Anthera announces that the Blisibimod CHABLIS-SC1 phase 3 study did not achieve the primary endpoint in patients with active systemic lupus erythematosus. 2016 http://investor.anthera.com/releasedetail.cfm?ReleaseID=998740 (Accessed May 30, 2017).
96 Yang M, Sun L, Wang S, *et al*. Novel function of B cell-activating factor in the induction of IL-10-producing regulatory B cells. *J Immunol* 2010;184:3321–5.
97 Klatzmann D, Abbas AK. The promise of low-dose interleukin-2 therapy for autoimmune and inflammatory diseases. *Nat Rev Immunol* 2015;15:283–94.
98 Saadoun D, Rosenzwajg M, Joly F, *et al*. Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. *N Engl J Med* 2011;365:2067–77.
99 Koreth J, Matsuoka K, Kim HT, *et al*. Interleukin-2 and regulatory T cells in graft-versus-host disease. *N Engl J Med* 2011;365:2055–66.
100 von Spee-Mayer C, Siegert E, Abdirama D, *et al*. Low-dose interleukin-2 selectively corrects regulatory T cell defects in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2016;75:1407–15.
101 Hartemann A, Bensimon G, Payan CA, *et al*. Low-dose interleukin 2 in patients with type 1 diabetes: a phase 1/2 randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2013;1:295–305.
102 Castela E, Le Duff F, Butori C, *et al*. Effects of low-dose recombinant interleukin 2 to promote T-regulatory cells in Alopecia Areata. *JAMA Dermatol* 2014;150:748–51.
103 Eastwood D, Findlay L, Poole S, *et al*. Monoclonal antibody TGN1412 trial failure explained by species differences in CD28 expression on CD4+ effector memory T-cells. *Br J Pharmacol* 2010;161:512–26.
104 Tyrsin D, Chuvpilo S, Matskevich A, *et al*. From TGN1412 to TAB08: the return of CD28 superagonist therapy to clinical development for the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2016;34(4 Suppl 98):45–8.
105 König M, Rharbaoui F, Aigner S, *et al*. Tregalizumab - A monoclonal antibody to target regulatory T cells. *Front Immunol* 2016;7:11.
106 De Groot AS, Moise L, McMurry JA, *et al*. Activation of natural regulatory T cells by IgG Fc-derived peptide "Tregitopes". *Blood* 2008;112:3303–11.
107 Cousens L, Najafian N, Martin WD, *et al*. Tregitope: immunomodulation powerhouse. *Hum Immunol* 2014;75:1139–46.
108 De Groot AS, Cousens L, Mingozzi F, *et al*. Tregitope peptides: the active pharmaceutical ingredient of IVIG? *Clin Dev Immunol* 2013;2013:1–6.
109 Bluestone JA, Buckner JH, Fitch M, *et al*. Type 1 diabetes immunotherapy using polyclonal regulatory T cells. *Sci Transl Med* 2015;7:315ra189.
110 Benham H, Nel HJ, Law SC, *et al*. Citrullinated peptide dendritic cell immunotherapy in HLA risk genotype-positive rheumatoid arthritis patients. *Sci Transl Med* 2015;7:290ra87.
111 Bell GM, Anderson AE, Diboll J, *et al*. Autologous tolerogenic dendritic cells for rheumatoid and inflammatory arthritis. *Ann Rheum Dis* 2017;76:227–34.
112 Sakaguchi S, Vignali DA, Rudensky AY, *et al*. The plasticity and stability of regulatory T cells. *Nat Rev Immunol* 2013;13:461–7.
113 Weinblatt M, Schiff M, Goldman A, *et al*. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. *Ann Rheum Dis* 2007;66:228–34.
114 Genovese MC, Cohen S, Moreland L, *et al*. Combination therapy with etanercept and Anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 2004;50:1412–9.
115 Weinblatt M, Combe B, Covucci A, *et al*. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. *Arthritis Rheum* 2006;54:2807–16.
116 Tiller KE, Tessier PM. Advances in antibody design. *Annu Rev Biomed Eng* 2015;17:191–216.
117 Fleischmann RM, Wagner F, Kivitz AJ, *et al*. FRI0188 Safety, Tolerability, and Pharmacodynamics of ABT-122, A Dual TNF- and IL-17–Targeted Dual Variable Domain (DVD)-IG™ in Patients with Rheumatoid Arthritis. *Ann Rheum Dis* 2016;75(Suppl 2):498.1–498.
118 Mease PJ, Genovese MC, Weinblatt M, *et al*. Safety and efficacy of ABT-122, a TNF and IL-17–Targeted Dual Variable Domain (DVD)–Ig™, in Psoriatic Arthritis Patients with Inadequate Response to Methotrexate: Results from a Phase 2 Trial [abstract].. *Arthritis Rheumatol* 2016;68 http://acrabstracts.org/abstract/safety-and-efficacy-of-abt-122-a-tnf-and-il-17-targeted-dual-variable-domain-dvd-ig-in-psoriatic-arthritis-patients-with-inadequate-response-to-methotrexate-results-from/.
119 Monteleone G, Fantini MC, Onali S, *et al*. Phase I clinical trial of Smad7 knockdown using antisense oligonucleotide in patients with active Crohn's disease. *Mol Ther* 2012;20:870–6.
120 Laudisi F, Dinallo V, Di Fusco D, *et al*. Smad7 and its potential as therapeutic target in inflammatory bowel diseases. *Curr Drug Metab* 2016;17:303–6.
121 Monteleone G, Neurath MF, Ardizzone S, *et al*. Mongersen, an oral SMAD7 antisense oligonucleotide, and Crohn's disease. *N Engl J Med* 2015;372:1104–13.
122 Torres T, Romanelli M, Chiricozzi A. A revolutionary therapeutic approach for psoriasis: bispecific biological agents. *Expert Opin Investig Drugs* 2016;25:751–4.
123 Isailovic N, Daigo K, Mantovani A, *et al*. Interleukin-17 and innate immunity in infections and chronic inflammation. *J Autoimmun* 2015;60:1–11.

OPEN ACCESS

EXTENDED REPORT

Arthroscopic partial meniscectomy versus placebo surgery for a degenerative meniscus tear: a 2-year follow-up of the randomised controlled trial

Raine Sihvonen,[1] Mika Paavola,[2] Antti Malmivaara,[3] Ari Itälä,[4] Antti Joukainen,[5] Heikki Nurmi,[6] Juha Kalske,[2] Anna Ikonen,[2] Timo Järvelä,[7] Tero A H Järvinen,[8] Kari Kanto,[1] Janne Karhunen,[2] Jani Knifsund,[4] Heikki Kröger,[5] Tommi Kääriäinen,[5] Janne Lehtinen,[1] Jukka Nyrhinen,[6] Juha Paloneva,[6] Outi Päiväniemi,[1] Marko Raivio,[1] Janne Sahlman,[5] Roope Sarvilinna,[2] Sikri Tukiainen,[2] Ville-Valtteri Välimäki,[2] Ville Äärimaa,[4] Pirjo Toivonen,[9] Teppo L N Järvinen,[9] The FIDELITY (Finnish Degenerative Meniscal Lesion Study) Investigators

For numbered affiliations see end of article.

Correspondence to
Professor Teppo L N Järvinen, Department of Orthopaedics and Traumatology, University of Helsinki and Helsinki University Hospital, Töölö Hospital, Topeliuksenkatu 5, Helsinki 00260, Finland; teppo.jarvinen@helsinki.fi

Received 19 January 2017
Revised 3 April 2017
Accepted 13 April 2017
Published Online First 18 May 2017

ABSTRACT

Objective To assess if arthroscopic partial meniscectomy (APM) is superior to placebo surgery in the treatment of patients with degenerative tear of the medial meniscus.

Methods In this multicentre, randomised, participant-blinded and outcome assessor-blinded, placebo-surgery controlled trial, 146 adults, aged 35–65 years, with knee symptoms consistent with degenerative medial meniscus tear and no knee osteoarthritis were randomised to APM or placebo surgery. The primary outcome was the between-group difference in the change from baseline in the Western Ontario Meniscal Evaluation Tool (WOMET) and Lysholm knee scores and knee pain after exercise at 24 months after surgery. Secondary outcomes included the frequency of unblinding of the treatment-group allocation, participants' satisfaction, impression of change, return to normal activities, the incidence of serious adverse events and the presence of meniscal symptoms in clinical examination. Two subgroup analyses, assessing the outcome on those with mechanical symptoms and those with unstable meniscus tears, were also carried out.

Results In the intention-to-treat analysis, there were no significant between-group differences in the mean changes from baseline to 24 months in WOMET score: 27.3 in the APM group as compared with 31.6 in the placebo-surgery group (between-group difference, −4.3; 95% CI, −11.3 to 2.6); Lysholm knee score: 23.1 and 26.3, respectively (−3.2; −8.9 to 2.4) or knee pain after exercise, 3.5 and 3.9, respectively (−0.4; −1.3 to 0.5). There were no statistically significant differences between the two groups in any of the secondary outcomes or within the analysed subgroups.

Conclusions In this 2-year follow-up of patients without knee osteoarthritis but with symptoms of a degenerative medial meniscus tear, the outcomes after APM were no better than those after placebo surgery. No evidence could be found to support the prevailing ideas that patients with presence of mechanical symptoms or certain meniscus tear characteristics or those who have failed initial conservative treatment are more likely to benefit from APM.

Linked

► http://dx.doi.org/10.1136/annrheumdis-2017-211664

CrossMark

To cite: Sihvonen R, Paavola M, Malmivaara A, *et al*. *Ann Rheum Dis* 2018;**77**:188–195.

INTRODUCTION

Arthroscopic partial meniscectomy (APM) is one of the most common orthopaedic operations,[1] with an incidence that has increased steadily from 1990s until late 2010s.[2–5] Most APMs are carried out in middle-aged and older patients with knee symptoms and degenerative knee disease.[1 2] Several recent meta-analyses based on randomised controlled trials (RCTs) have failed to show a treatment-benefit of APM over conservative treatment or placebo surgery for these patients.[6–10]

Aligned with the evidence, most guidelines and expert opinion now refrain from recommending APM as the first-line treatment for patients with a degenerative meniscus tear, but still advocate surgery after a failed attempt of conservative treatment.[11–16] Such recommendations rest on three issues: generally favourable clinical experience, some before-after studies on patients undergoing APM due to persisting symptoms despite conservative treatment[17 18] and particularly the evidence from three RCTs[19–21] in which one-third of participants initially allocated to non-surgical treatment opted for crossing over to APM due to persisting knee symptoms or insufficient improvement. After undergoing APM, participants achieved similar outcomes compared with those initially assigned to surgery and those responding favourably to initial non-surgical/conservative treatment.[19–21] These findings have been interpreted as evidence that APM should be performed after failed conservative treatment.[22] Although such hypotheses might well be true, an alternative accounting can explain the number of crossovers and the beneficial treatment effects of surgery after failed conservative treatment: lack of blinding (participants' knowledge of not having undergone surgery) may drive conservatively treated patients to request surgery and also make them feel more content with the outcome once having undergone surgery.[23 24]

In addition to patients failing to improve after conservative treatment, other subgroups considered to benefit from APM are those with so-called 'mechanical symptoms'[25–28] or those with 'unstable' meniscal tear.[15 17 28]

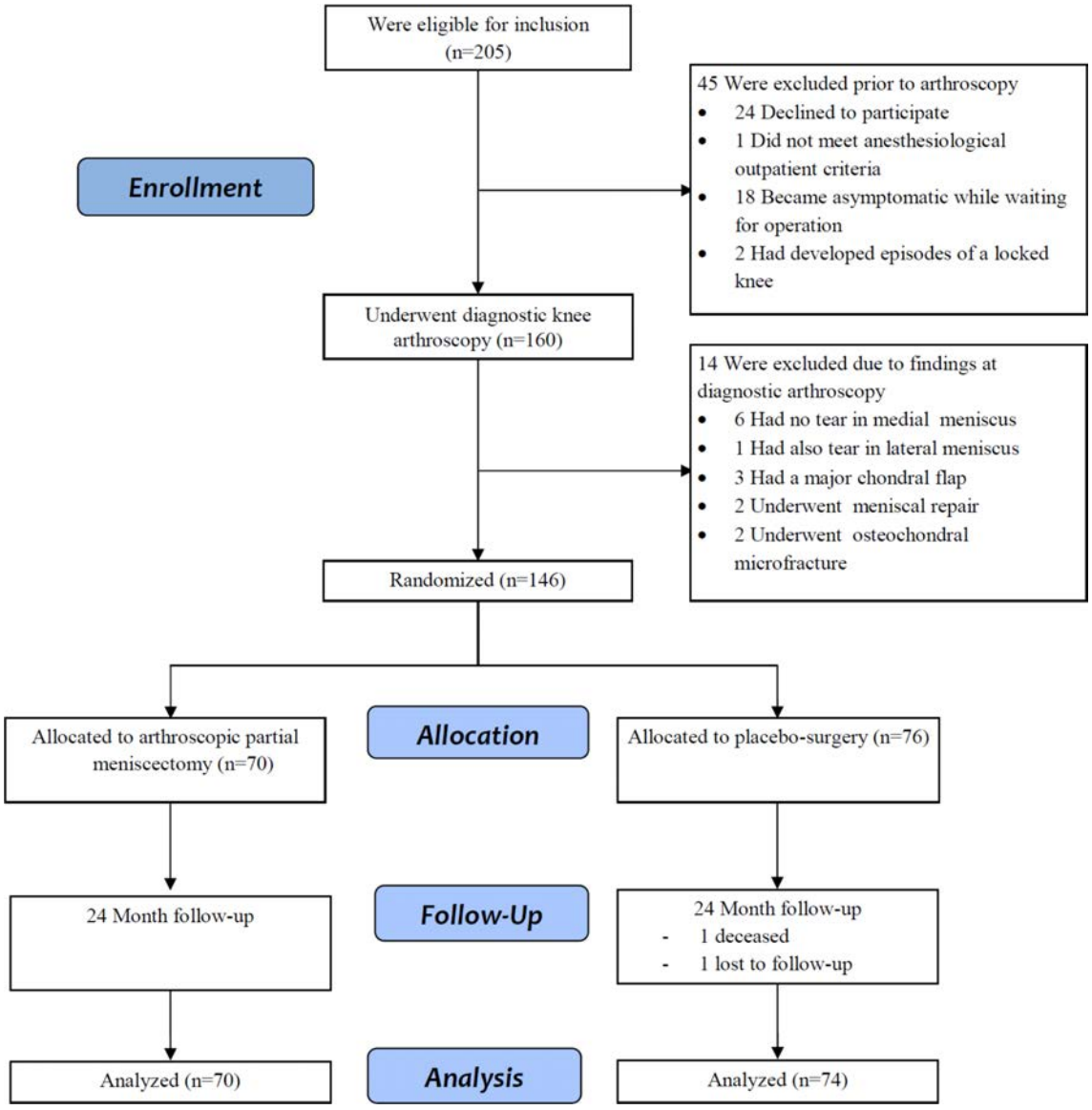


Figure 1 Participant enrolment flow diagram.

Accordingly, the aim of this extension of our recently published Finnish Degenerative Meniscal Lesion Study (FIDELITY) trial[29] was twofold: (a) to assess if APM is superior over placebo surgery over the course of 24-month follow-up determined using patient relevant outcomes, the frequency of unblinding of the treatment-group allocation and clinical examination of the knee and (b) to assess whether our data corroborates or refutes common assertions regarding existence of subgroups of patients likely to benefit from APM.

MATERIALS AND METHODS

We conducted a multicentre, randomised, participant-blinded and outcome assessor-blinded, placebo-surgery controlled efficacy trial involving participants aged 35–65 years with knee symptoms over 3 months, consistent with degenerative medial meniscus tear and unresponsive to conventional conservative treatment and no clinical[30] or radiographic (Kellgren-Lawrence grade ≤1)[31] knee osteoarthritis. The study took place in five orthopaedic centres in Finland during the period from December 2007 through March 2014. All patients had a suspicion of a meniscus tear based on symptoms and clinical tests, a tear that was later verified on both MRI and knee arthroscopy. Patients with an obvious trauma-induced onset of symptoms or with a recent history of a locked knee were excluded from the trial. On entering the study, participants were informed that they would be allowed to consider a reoperation 6 months or later after the procedure if they did not have adequate relief of symptoms.

Participants first underwent diagnostic knee arthroscopy and then (during the same operation) were assigned to APM or placebo surgery. For the randomisation, the sequentially numbered, opaque, sealed envelopes were prepared by a statistician. Randomisation was performed in a 1:1 ratio with a block size of 4, and with stratification according to study site, age (35–50 or 51–65 years), sex and the absence or presence of minor degenerative changes on a radiograph (Kellgren-Lawrence grade 0 or 1, respectively).

The participants, all caregivers and those assessing the outcomes were blinded to the treatment assignment. Participants were followed-up by questionnaires at 2, 6, 12 and 24 months. At the 24-month follow-up, all participants were also clinically examined by an independent orthopaedic surgeon unaware of the treatment allocation. Standardised clinical examination included clinical meniscal tests[32]: McMurray test,[33] pain provoked by joint line palpation and pain provoked by forced

flexion and varus. Also, range of knee motion, knee crepitus, bony enlargement, effusion, location of pain at palpation and knee stability was recorded.

The study was registered at ClinicalTrials.gov (NCT00549172). We have described the design[34] and published the 12-month results[29] of the trial previously. The protocol was approved by the institutional review board of the Pirkanmaa Hospital District (R 06157). The study was conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent.

Interventions

Arthroscopic evaluation included recording the presence of intra-articular pathology (meniscus tears, loose bodies and characterisation of chondral lesions of both tibiofemoral and patellofemoral chondral surfaces) according to the International Cartilage Repair Society cartilage injury classification scale[35] and the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine classification of meniscal tears.[36]

During the APM, the damaged and loose parts of the meniscus were removed with the use of arthroscopic instruments until solid meniscal tissue was reached with preservation of as much of the meniscus as possible. No other surgical procedure was performed. For the placebo surgery, APM was simulated to mimic the sensations and sounds of a true APM. The participants were also kept in the operating room for the amount of time required to perform an actual APM.

In both the APM and the placebo-surgery groups, postoperative care was delivered according to a standardised protocol specifying that all participants receive the same walking aids and instructions for the same graduated home-based exercise programme.

Outcomes

Primary outcomes were the change in Western Ontario Meniscal Evaluation Tool (WOMET), the Lysholm knee score and pain after exercise from baseline to 24 months after surgery. The WOMET[37] is a meniscus-specific health-related quality-of-life instrument, validated especially for patients with a degenerative meniscal tear.[38] The Lysholm knee score is a validated, condition-specific outcome measure.[39 40] WOMET and Lysholm scores each range from 0 to 100, with 0 indicating the most severe symptoms and 100 the absence of symptoms. Knee pain (during the preceding week) was assessed on an 11-point numerical rating scale ranging from 0 (no pain) to 10 (extreme pain).

As a secondary outcome, the frequency of patients in the two treatment groups who did not have adequate relief of symptoms and whose treatment-group allocation was therefore unblinded was determined. Participants were also asked to respond to the following questions: “Are you satisfied with your knee at present?” and “ Is your knee better than before the intervention?” on a 5-point Likert scale. As before,[41] the responses ‘very satisfied’ or ‘satisfied’ were categorised as satisfied, while responses ‘neither satisfied nor dissatisfied’, ‘dissatisfied’ and ‘very dissatisfied’ were categorised as dissatisfied. Similar to satisfaction, the responses ‘much better’ and ‘better’ were considered to indicate improvement, while responses ‘unchanged’, ‘worse’ or ‘much worse’ were deemed not improved. Serious adverse events were registered. In addition, the participants were asked whether or not they were able to return to their previous activities. Finally, the frequency of participants with a positive meniscus test at clinical examination was assessed.

APM was also compared with placebo surgery within two subgroups of participants, those with mechanical symptoms of the knee and those with unstable meniscus tear. The presence of mechanical symptoms was assessed using the locking domain question of the Lysholm knee score.[39] In brief, we asked patients to choose one out of five following responses that best reflected the status of their knee: i) no locking or catching, ii) catching sensations but no locking, iii) occasional locking, iv) frequent locking or v) locked at present. Meniscus tears with longitudinal tear pattern, bucket handle tear or flap were determined as unstable, whereas radial, horizontal and complex were determined as stable.[13]

Table 1 Baseline characteristics of the participants allocated to APM or placebo surgery. Values are numbers (percentages), means±SD or medians (ranges)

	APM (n=70)	Placebo surgery (n=76)
Sex		
Female	28 (40)	29 (38)
Male	42 (60)	47 (62)
Age (years)	52.1±6.9	52.0±7.2
Body mass index (kg/m^2)	26.9±4.0	27.9±4.0
Duration of symptoms (months)	10 (3–50)	10 (3–47)
Kellgren-Lawrence grade*		
0	35 (50)	36 (47)
1	35 (50)	40 (53)
Meniscal tests		
Positive McMurray test†	16 (23)	15 (20)
Pain provoked by forced flexion and compression	50 (71)	59 (78)
Pain provoked by palpation at the joint line	63 (90)	74 (97)
Symptoms of catching or locking	32 (46)	37 (49)
Unstable tear at knee arthroscopy‡	34 (49)	41 (54)
WOMET score§	56.4±17.3	52.8±18.1
Lysholm score¶	60.2±14.7	60.1±14.6
Pain after exercise (VAS)**	5.8±2.0	6.1±2.0

*The Kellgren-Lawrence scale is a radiographic classification of the severity of knee osteoarthritis. Grade 0 denotes no abnormalities and grade 1 denotes minor degenerative changes (doubtful narrowing of the joint space or possible osteophytic lipping).
†Results of a McMurray test are positive if a ‘click’ over the medial tibiofemoral joint line is felt by the examiner during flexion and extension of the knee under varus stress.
‡Longitudinal, bucket handle or flap tear at arthroscopy.
§The WOMET contains 16 items addressing three domains: 9 items addressing physical symptoms; 4 items addressing disabilities with regard to sports, recreation, work and lifestyle and 3 items addressing emotions. The score indicates the percentage of a normal score; therefore, 100 is the best possible score and 0 is the worst possible score.
¶The Lysholm knee score is based on an eight-item questionnaire designed to evaluate knee function and symptoms in activities of daily living. Scores range from 0 to 100; higher scores indicate less severe symptoms.
**Knee pain after exercise (during the preceding week) was assessed on a rating scale of 0–10, with 0 denoting no pain and 10 denoting extreme pain.
APM, arthroscopic partial meniscectomy; WOMET, Western Ontario Meniscal Evaluation Tool; VAS, visual analogue scale.

Patient involvement

There was no active patient involvement in the design of the study, in the recruitment to or conduct of the study. However, one of the main outcome measures (the WOMET) was initially developed with a patient-centred approach: the items included in the final version of the questionnaire were those identified by patients to impact most significantly on their quality of life.[37] The results of this RCT will be conveyed to the participants in lay language in a pamphlet distributed by mail after the 5-year follow-up.

Table 2 Primary outcomes of the trial at 24-month follow-up. Values are means with 95% CIs

Primary outcomes	APM (n=70)	Placebo surgery (n=74)	Improvement from baseline		Between-Group Difference in Improvement from Baseline
			APM	Placebosurgery	
Unadjusted					
WOMET score*	83.7 (79.0 to 88.3)	83.9 (79.9 to 87.9)	27.3 (22.1 to 32.4)	31.6 (26.9 to 36.3)	−4.3 (−11.3 to 2.6)
Lysholm knee score†	83.3 (79.5 to 87.1)	85.9 (83.1 to 88.8)	23.1 (18.8 to 27.4)	26.3 (22.6 to 30.0)	−3.2 (−8.9 to 2.4)
Pain after exercise‡	2.3 (1.7 to 2.9)	2.3 (1.7 to 2.9)	3.5 (2.8 to 4.2)	3.9 (3.3 to 4.6)	−0.4 (−1.3 to 0.5)
Adjusted§					
WOMET score	80.9 (75.4 to 86.5)	86.1 (80.5 to 91.8)	26.6 (21.1 to 32.2)	31.8 (26.2 to 37.5)	−5.2 (−13.1 to 2.7)
Lysholm knee score	82.2 (78.2 to 86.3)	86.5 (82.3 to 90.6)	22.3 (18.3 to 26.3)	26.6 (22.4 to 30.7)	−4.3 (−10.0 to 1.5)
Pain after exercise	2.3 (1.5 to 3.1)	1.9 (1.1 to 2.7)	3.7 (2.9 to 4.5)	4.1 (3.3 to 4.9)	−0.4 (−1.5 to 0.7)

*The WOMET contains 16 items addressing three domains: 9 items addressing physical symptoms; 4 items addressing disabilities with regard to sports, recreation, work and lifestyle and 3 items addressing emotions. The score indicates the percentage of a normal score; therefore, 100 is the best possible score and 0 is the worst possible score.
†The Lysholm knee score is based on an eight-item questionnaire designed to evaluate knee function and symptoms in activities of daily living. Scores range from 0 to 100; higher scores indicate less severe symptoms.
‡Knee pain after exercise (during the preceding week) was assessed on a rating scale of 0–10, with 0 denoting no pain and 10 denoting extreme pain.
§Values are adjusted with the baseline score, study site, age, sex and the absence or presence of minor degenerative changes on a radiograph (Kellgren–Lawrence grade 0 or 1, respectively).
APM, arthroscopic partial meniscectomy; WOMET, Western Ontario Meniscal Evaluation Tool.

Statistical methods

The trial was designed to ascertain whether APM is superior to placebo surgery in treating patients with knee pain and a degenerative meniscus tear. Baseline characteristics were analysed with the use of descriptive statistics. For the primary analysis, the change in each score (mean with 95% CI) from baseline to 24 months was compared between the two study groups. This analysis was also performed after adjustment for the baseline score and for the stratifying variables used for randomisation. The study was powered to detect a minimal clinically important improvement in the WOMET and Lysholm scores (described as improvements of at least 15.5 and 11.5 points, respectively) and in the score for knee pain after exercise (improvement of at least 2.0 points).[34] For the secondary analyses, the frequency of assessed outcomes were compared between the two groups. Two subgroup analyses were carried out, for those with mechanical symptoms and for those with unstable meniscus tear; p values for interaction were calculated for the subgroup analyses.

A Student's t-test and non-parametric test (Mann-Whitney U test) were used to compare continuous variables (normally distributed and not normally distributed, respectively) between the groups, and Fisher's exact test was used with binomial and categorical variables. All statistical analyses were performed on an intention-to-treat basis; as the frequency of crossover was low, no per-protocol analysis was performed. A p value of 0.05 was considered to indicate statistical significance. SPSS Statistics, V.23 (IBM), was used for all statistical analyses.

RESULTS

The flow chart of the trial is shown in figure 1. Of the 205 eligible patients, 146 underwent randomisation; 70 were assigned to APM and 76 to placebo surgery. The baseline characteristics of the two groups were similar. On average, half of the participants in both groups reported mechanical symptoms preoperatively. There were 34 participants with a tear morphology defined as 'unstable' in the APM group and 41 in the placebo-surgery group (table 1). There were 24 patients who were eligible but declined to participate in the study. They were similar to those who underwent randomisation with respect to age, sex and body mass index at baseline, and all of them underwent arthroscopic partial meniscectomy. At the 24-month follow-up, two participants were lost to follow-up (one not responding to contact attempts and one deceased), both from the placebo-surgery group.

Both groups showed a marked improvement in all primary outcomes. However, the difference between the two groups did not reach statistical significance and 95% CIs excluded clinically relevant effect in any of the three primary outcomes over the course of the 24-month follow-up (table 2 and figure 2). Five participants (7.1%) in the APM group and seven (9.2%) in the placebo-surgery group complained of symptoms severe enough to result in the unblinding of the treatment-group allocation (p=0.767). Most of the participants, in both groups, were satisfied and reported improvement with no statistically significant difference between the two treatment groups. One participant in the APM group had a serious adverse event (a knee infection 4 months after the initial operation). No between-group difference was observed in the participants' frequency in returning to normal activity level or in the frequency of mechanical symptoms. No statistically significant difference was found between the two groups in the meniscal tests during clinical examination either (table 3). The outcome of the patients who declined to participate (n=17, five lost to follow-up) were similar with those randomised, excluding the change in WOMET score (SD), which was greater for those declined (43.2±22.4) as compared with those randomised (29.5±21.1) with a between-group difference −13.7 (95% CI −25.6 to −2.9).

In the two subgroup analyses, one assessing the effect of preoperative mechanical symptoms and the other the effect of unstable tear on the treatment outcome, there was no difference in any of the primary or secondary outcomes between the APM and placebo-surgery groups (tables 4 and 5).

DISCUSSION

In this extension of the FIDELITY trial,[29] we found no statistically significant difference between the APM and placebo surgery for symptomatic patients with a degenerative meniscus tear and no osteoarthritis (OA) in any of the used outcome measures over the course of 24-month follow-up. No evidence could be found to support the prevailing ideas that patients with presence of mechanical symptoms or certain meniscus tear characteristics or those who failed initial conservative treatment are more likely to benefit from APM.

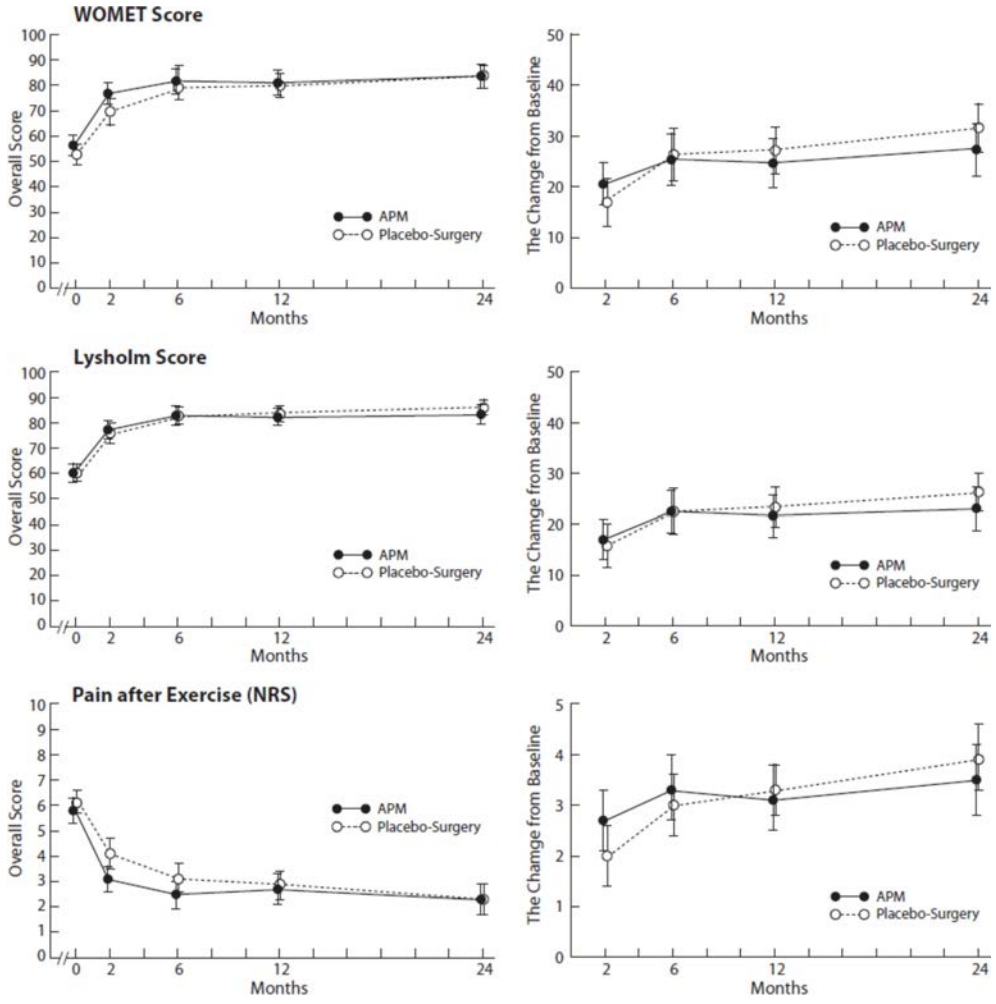


Figure 2 Mean values with 95% CIs in all three primary scores during the 24-month follow-up for both groups. APM, arthroscopic partial meniscectomy; NRS, numerical rating scale; WOMET, Western Ontario Meniscal Evaluation Tool.

The strengths of the FIDELITY trial have been elaborated in detail previously.[29 34] In brief, our study was a multicentre, randomised, placebo-controlled efficacy trial with a 2-year follow-up. Controlling for the possible placebo effects of surgery requires that besides participants, all caregivers and outcome assessors are blinded to the treatment allocation.[42] The use of multiple validated outcomes covering many different possible symptoms related to degenerative knee and meniscus tear can also be considered strength of this trial.

Table 3 Secondary outcomes of the trial at 24-month follow-up. Values are numbers (percentage)

Outcome	APM (n=70)	Placebo surgery (n=74)	P Value
Satisfied patients	54 (77.1)	58 (78.4)	1.000
Improved patients	61 (87.1)	63 (85.1)	0.812
Treatment-group unblinding	5 (7.1)	7 (9.2)	0.767
Reoperations	4 (5.7)	7 (9.2)	0.537
Arthroscopy	2 (2.9)	6 (7.9)	0.279
HTO/TKR	2 (2.9)	1 (1.3)	0.607
Returned to normal activities	50 (72.5)	58 (78.4)	0.442
Serious adverse events	1 (1.4)	0	0.479
Mechanical symptoms	18 (25.7)	15 (20.3)	0.552
Meniscal tests			
Positive McMurray test	6 (8.6)	5 (6.8)	0.760
Pain provoked by forced flexion and compression	8 (11.4)	10 (13.5)	0.803
Pain provoked by palpation at the joint line	22 (31.4)	21 (28.8)	0.855
At least one positive meniscal test	26 (37.1)	25 (33.8)	0.729

HTO, high tibial osteotomy; TKR, total knee replacement.

The strengths of the FIDELITY trial have been elaborated in detail previously.[29 34] In brief, our study was a multicentre, randomised, placebo-controlled efficacy trial with a 2-year follow-up. Controlling for the possible placebo effects of surgery requires that besides participants, all caregivers and outcome assessors are blinded to the treatment allocation.[42] The use of multiple validated outcomes covering many different possible symptoms related to degenerative knee and meniscus tear can also be considered strength of this trial.

There are also some limitations worth discussing. We excluded patients with a truly 'traumatic' onset of symptoms, so our results are only directly applicable to patients with non-traumatic meniscus tears. Obviously, the concepts 'degenerative' or 'traumatic' in the context of meniscal injuries are very vague by nature. In this trial, all patients with sudden injuries related to their own voluntary muscle activities (such as kneeling, bending or kicking) and patients with a minor twisting of the knee were included. In essence, our criteria for labelling a tear as 'traumatic' required a more substantial event, such as falling from a chair, stairs or bicycle, or slipping on ice. In this context, to our knowledge, the only study specifically testing the assumption that meniscal tear outcomes would be any better for those with a traumatic onset of symptoms than for those without does not support such hypothesis.[43] Moreover, a very recent study showed that patients with traumatic meniscal tears do not experience greater improvements in patient-reported outcomes after APM than patients with degenerative tears.[44]

The generalisability of the FIDELITY trial has been questioned.[25 45 46] Although the design of the FIDELITY has been elaborated in detail previously,[34] it is worth reasserting that it was

Table 4 Primary and secondary outcomes at 24-month follow-up for the subgroup of patients with mechanical symptoms at baseline. Values are means with 95% CIs and numbers (percentage)

	APM (n=32)	Placebo surgery (n=37)	Improvement from baseline		Between-Group Difference in Improvement from Baseline or P value
Primary outcomes			**APM**	**Placebo surgery**	
WOMET score	79.9 (72.4 to 87.5)	86.4 (81.5 to 91.3)	27.6 (18.0 to 37.1)	37.4 (30.1 to 44.7)	−9.8 (−21.5 to 1.8)
Lysholm knee score	81.8 (75.8 to 87.7)	86.9 (82.8 to 91.0)	28.3 (21.0 to 35.5)	34.1 (28.8 to 39.4)	−5.9 (−14.6 to 2.8)
Pain after exercise	2.6 (1.7 to 3.5)	1.9 (1.2 to 2.6)	3.3 (2.2 to 4.4)	4.5 (3.7 to 5.3)	−1.2 (−2.5 to 0.2)
Secondary outcomes					
Satisfied patients	25 (78.1)	30 (81.1)			p=0.774
Improved patients	27 (84.4)	33 (89.2)			p=0.723
Treatment-group unblinding	2 (6.3)	1 (2.7)			p=0.593
Returned to normal activities	20 (64.5)	29 (78.4)			p=0.279
Mechanical symptoms	11 (34.4)	11 (29.7)			p=0.797
At least one positive meniscal test	14 (43.8)	14 (37.8)			p=0.633

One patient missing return to activity in APM group (n=31). p Values for interaction (randomisation and mechanical symptoms) were 0.113, 0.268 and 0.097 for the change in WOMET score, Lysholm knee score and pain after exercise, respectively.
APM, arthroscopic partial meniscectomy; WOMET, Western Ontario Meniscal Evaluation Tool.

designed as an *efficacy* trial to test the therapeutic potential of APM. Accordingly, we recruited a sample that potentially would have an 'optimal response' to APM (medial meniscus tear, no OA). Such patients are rare to find among ordinary patients with a degenerative meniscus tear. This explains the lengthy recruitment period (4 years) despite five high-volume centres, but given our finding of lack of efficacy, this methodological choice actually increases —rather than diminishes—the generalisability of our study.

Some have criticised the FIDELITY trial for recruiting patients with symptoms that were not attributable to a meniscal tear,[25] yet our subjects' eligibility was confirmed by both MRI and arthroscopy. APM is typically advocated for patients with knee symptoms in whom a tear is confirmed by MRI, particularly those without concomitant knee osteoarthritis.[47] Increasing evidence, however, suggests that a degenerative meniscal tear may be an early sign of knee osteoarthritis rather than a separate clinical problem that causes symptoms.[48–50] Moreover, specific meniscal pathology and other structural joint pathologies found at meniscal surgery were not associated with preoperative self-reported pain and function in patients with meniscal tears.[51] We interpret our findings as supportive of the idea that degenerative meniscus tear does not cause specific symptoms even in knees without osteoarthritis.[52]

We are also aware of the limitations related to post hoc subgroup analyses[53]: the number of participants in our subgroups was small, the analyses were not planned a priori and there was no formal power calculation. However, as patients with mechanical symptoms and with unstable tear have been—and still are—widely suggested as *the ideal subgroup* to benefit from APM[25 27 54–56] and the hypothesis is backed by a credible biological rationale, we felt that our analyses were of high clinical relevance.[53]

We set out to address a few apparent gaps in the existing evidence base regarding arthroscopic surgery for patients with knee pain and degenerative meniscus tear/knee disease. First, although a 24-month follow-up is a commonly held 'minimal requirement' for any procedure in orthopaedics, only three[19 57 58] of the eight previous RCTs on this topic have followed-up patients longer than 12 months. Our 24-month data show that most of the improvement observed with both APM and placebo surgery was evident already at 6 months after surgery and the extended follow-up did not have an effect on our primary finding.[29] Second, many authors and organisations

Table 5 Primary and secondary outcomes at 24-month follow-up for the subgroup of patients with unstable meniscus tear. Values are means with 95% CIs and numbers (percentage)

	APM (n=34)	Placebo surgery (n=39)	Improvement from baseline (or 24mo)		Between-Group Difference in Improvement from Baseline or P value
Primary outcomes			**APM**	**Placebo surgery**	
WOMET score	84.6 (78.0 to 91.3)	84.5 (78.9 to 90.0)	27.7 (19.5 to 35.9)	33.3 (27.5 to 39.1)	−5.6 (−15.3 to 4.1)
Lysholm knee score	84.5 (78.7 to 90.3)	86.7 (83.2 to 90.3)	23.4 (16.7 to 30.2)	27.5 (22.6 to 32.4)	−4.0 (−12.1 to 4.0)
Pain after exercise	2.2 (1.4 to 3.0)	2.2 (1.5 to 3.0)	3.5 (2.6 to 4.4)	4.1 (3.2 to 4.9)	−0.6 (−1.8 to 0.6)
Secondary outcomes					
Treatment-group unblinding	3 (8.8%)	3 (7.3%)			p=1.000
Satisfied patients	26 (76.5%)	31 (79.5%)			p=0.784
Improved patients	30 (88.2%)	35 (89.7%)			p=1.000
Returned to normal activities	23 (67.6%)	30 (76.9%)			p=0.436
Mechanical symptoms	8 (23.5)	10 (25.6)			p=1.000
At least one positive meniscal test	10 (29.4)	13 (33.3)			p=0.803

Two patients lost to follow-up, both in placebo-surgery group. p Values for interaction (randomisation and unstable tear) were 0.701, 0.754 and 0.623 for the change in WOMET score, Lysholm knee score and pain after exercise, respectively.
APM, arthroscopic partial meniscectomy; WOMET, Western Ontario Meniscal Evaluation Tool.

advocate APM for patients 'unresponsive to conservative treatment',[12–16] a strategy based on the previous *unblinded* trials.[19–21] These trials showed that about 30% of participants initially allocated to conservative treatment have opted to crossover to surgery due to persisting symptoms. Although such behaviour is intuitively rational, it should be recalled that when patients are told of the possibility of surgical treatment but are allocated to conservative care, this so-called 'failed opportunity' may drive patients to seek surgery if symptoms persist.[42] In our *blinded* trial, the frequency of unblinding of the treatment-group allocation due to persisting symptoms was clearly lower than in the previous—unblinded—studies and we found no difference between our two treatment groups. Our data thus highlight the vital importance of proper blinding of study participants in surgical RCTs. Considering the rationale to carry out APM on those having failed previous conservative treatment further, a recent study comparing exercise therapy to APM alone (with no postoperative rehabilitation) showed that although 19% of participants allocated to exercise therapy crossed over to surgery during the 2-year follow-up, APM did not result in any additional benefit for them.[58]

Another widely held assertion is that the presence of mechanical symptoms (sensation of knee catching or locking) represents a valid indication for arthroscopic surgery.[25–27 59] This is premised on a rationale that mechanical symptoms are caused by a joint structure lodging between the gliding articular surfaces. Our recently published secondary analysis (1-year follow-up of this trial) showed that resection of a torn meniscus has no added benefit over placebo surgery in relieving knee catching or occasional locking.[60] The findings of this 2-year extension corroborate our previous findings. The absence of an effect of APM on patients with mechanical symptoms is also supported by previous subgroup analyses of controlled trials[21 61] and our own recent prospective cohort study of 900 consecutive patients undergoing APM.[62] With respect to the present data, patients with a true locked knee (unable to extend their knee fully) were excluded from the FIDELITY and thus some caution may be warranted in the interpretation of our current findings. Finally, meniscus tear morphology is often asserted to explain the success of APM,[17 28 63 64] but our data fail to support such notion.

In conclusion, the results of this randomised, placebo-controlled trial with 24 months follow-up show that APM provides no significant benefit over placebo surgery in patients with a degenerative meniscal tear and no knee osteoarthritis. These results support the evolving consensus that degenerative meniscus tear represents an (early) sign of knee osteoarthritis, rather than a clinical entity on its own, and accordingly, caution should be exercised in referring patients with knee pain and suspicion of a degenerative meniscal tear to MRI examination or APM, even after a failed attempt of conservative treatment.

Unanswered questions and future research

Arthroscopic surgery for knee pain in middle-aged and older patients is one of the most rigorously studied orthopaedic procedures. The evidence base shows very consistently that APM offers no benefit over conservative treatment or placebo surgery.[65] Still, hundreds of thousands of procedures are performed worldwide each year. Given the mounting evidence, anyone still advocating APMs should promptly launch methodologically rigorous, practical, real-world trial(s) embedded in the flow of practice to prove that APM truly works in the asserted subgroups of patients.

Author affiliations
[1]Department of Orthopedics and Traumatology, Hatanpää Hospital, Tampere, Finland
[2]Department of Orthopedics and Traumatology, Helsinki University Hospital, Helsinki, Finland
[3]Center for Health and Social Economics, National Institute for Health and Welfare, Helsinki, Finland
[4]Department of Orthopedics and Traumatology, Turku University Hospital, Turku, Finland
[5]Department of Orthopedics and Traumatology, Kuopio University Hospital, Kuopio, Finland
[6]Department of Orthopedics and Traumatology, Central Finland Central Hospital, Jyväskylä, Finland
[7]Arthroscopic and Sports Medicine Center Pohjola Sairaala, Helsinki, Finland
[8]Department of Orthopedics and Traumatology, Tampere University Hospital, Tampere, Finland
[9]Department of Orthopaedics and Traumatology, Helsinki University, Töölö Hospital, Helsinki, Finland

Acknowledgements We thank the patients for their participation. We would like to thank research nurses Marja-Liisa Sutinen, Sari Karesvuori, Pekka Karppi, Saara-Maija Hinkkanen, Johanna Koivistoinen, Kirsi Saarioja, Elina Jalava, Ina Fagerlund and Marketta Rautanen for their vital role in the implementation of the study.

Contributors The Finnish Degenerative Meniscal Lesion Study (FIDELITY) trial (patient enrolment and execution of follow-up assessments in 2007–2015) is carried out by the FIDELITY Investigators. Conception and design: RS, MP, AM and TLNJ. Analysis and interpretation of the data: RS and TLNJ. Drafting of the article: RS and TLNJ. Critical revision of the article for important intellectual content and final approval: all authors. Ensuring the accuracy of the work: RS and TLNJ. Obtaining of funding: TLNJ. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding This study was supported by the Jane and Aatos Erkko Foundation, the Sigrid Juselius Foundation, the State funding for university-level health research (Tampere and Helsinki University Hospitals), the Social Insurance Institution of Finland (KELA) and the Academy of Finland. Dr Sihvonen is supported also by The Finnish Medical Foundation and Orion-Pharmos Research Foundation. The funding sources had no role in in the collection, analysis and interpretation of data; in the writing of the report and in the decision to submit the article for publication.

Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Given that the informed consent forms of the Finnish Degenerative Meniscal Lesion Study trial did not include a provision for data sharing (trial launched in 2007), the full dataset cannot be shared due to a potential breach of the Finnish Personal Data Act. Scientists with a specific question regarding the trial data are encouraged to contact the corresponding author (TLNJ).

REFERENCES

1 Cullen KA, Hall MJ, Golosinskiy A. Ambulatory surgery in the United States, 2006. *Natl Health Stat Report* 2009;11:1–25.
2 Abrams GD, Frank RM, Gupta AK, *et al*. Trends in meniscus repair and meniscectomy in the United States, 2005-2011. *Am J Sports Med* 2013;41:2333–9.
3 Thorlund JB, Hare KB, Lohmander LS. Large increase in arthroscopic meniscus surgery in the middle-aged and older population in Denmark from 2000 to 2011. *Acta Orthop* 2014;85:287–92.
4 Kim S, Bosque J, Meehan JP, *et al*. Increase in outpatient knee arthroscopy in the United States: a comparison of National surveys of ambulatory surgery, 1996 and 2006. *J Bone Joint Surg Am* 2011;93:994–1000.
5 Montgomery SR, Zhang A, Ngo SS, *et al*. Cross-sectional analysis of trends in meniscectomy and meniscus repair. *Orthopedics* 2013;36:e1007–e1013.
6 Khan M, Evaniew N, Bedi A, *et al*. Arthroscopic surgery for degenerative tears of the meniscus: a systematic review and meta-analysis. *CMAJ* 2014;186:1057–64.
7 Thorlund JB, Juhl CB, Roos EM, *et al*. Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms. *BMJ* 2015;350:h2747.

8 Lamplot JD, Brophy RH. The role for arthroscopic partial meniscectomy in knees with degenerative changes: a systematic review. *Bone Joint J* 2016;98-B:934–8.
9 Monk P, Garfjeld Roberts P, Palmer AJ, *et al*. The Urgent Need for evidence in arthroscopic meniscal surgery: a systematic review of the evidence for Operative Management of Meniscal Tears. *Am J Sports Med* 2016.
10 van de Graaf VA, Wolterbeek N, Mutsaerts EL, *et al*. Arthroscopic partial meniscectomy or conservative treatment for Nonobstructive Meniscal Tears: a systematic review and Meta-analysis of Randomized Controlled Trials. *Arthroscopy* 2016;32:1855–65.
11 Katz JN, Jones MH. Treatment of meniscal tear: the more we learn, the less we Know. *Ann Intern Med* 2016;164:503.
12 Howell R, Kumar NS, Patel N, *et al*. Degenerative meniscus: Pathogenesis, diagnosis, and treatment options. *World J Orthop* 2014;5:597–602.
13 Mordecai SC, Al-Hadithy N, Ware HE, *et al*. Treatment of meniscal tears: an evidence based approach. *World J Orthop* 2014;5:233–41.
14 Carr AJ, Price AJ, Glyn-Jones S, *et al*. Advances in arthroscopy-indications and therapeutic applications. *Nat Rev Rheumatol* 2015;11:77–85.
15 Price A, Beard D. Arthroscopy for degenerate meniscal tears of the knee. *BMJ* 2014;348:g2382.
16 Katz JN, Losina E. Arthroscopic partial meniscectomy for degenerative tears: where do we stand? *Osteoarthritis Cartilage* 2014;22:1749–51.
17 El Ghazaly SA, Rahman AA, Yusry AH, *et al*. Arthroscopic partial meniscectomy is superior to physical rehabilitation in the management of symptomatic unstable meniscal tears. *Int Orthop* 2015;39:769–75.
18 Hutt JR, Craik J, Phadnis J, *et al*. Arthroscopy for mechanical symptoms in osteoarthritis: a cost-effective procedure. *Knee Surg Sports Traumatol Arthrosc* 2015;23:3545–9.
19 Herrlin SV, Wange PO, Lapidus G, *et al*. Is arthroscopic surgery beneficial in treating non-traumatic, degenerative medial meniscal tears? A five year follow-up. *Knee Surg Sports Traumatol Arthrosc* 2013;21:358–64.
20 Katz JN, Brophy RH, Chaisson CE, *et al*. Surgery versus physical therapy for a meniscal tear and osteoarthritis. *N Engl J Med* 2013;368:1675–84.
21 Gauffin H, Tagesson S, Meunier A, *et al*. Knee arthroscopic surgery is beneficial to middle-aged patients with meniscal symptoms: a prospective, randomised, single-blinded study. *Osteoarthritis Cartilage* 2014;22:1808–16.
22 Katz JN, Wright J, Spindler KP, *et al*. Predictors and outcomes of Crossover to surgery from physical therapy for Meniscal Tear and Osteoarthritis: a Randomized Trial comparing physical therapy and surgery. *J Bone Joint Surg Am* 2016;98:1890–6.
23 Buchbinder R. Meniscectomy in patients with knee osteoarthritis and a meniscal tear? *N Engl J Med* 2013;368:1740–1.
24 Katz JN. Surgery for lumbar spinal stenosis: informed patient preferences should weigh heavily. *Ann Intern Med* 2015;162:518–9.
25 Krych AJ, Carey JL, Marx RG, *et al*. Does arthroscopic knee surgery work? *Arthroscopy* 2014;30:544–5.
26 Stuart MJ, Lubowitz JH. What, if any, are the indications for arthroscopic debridement of the osteoarthritic knee? *Arthroscopy* 2006;22:238–9.
27 Jevsevar DS, Yates AJ, Sanders JO. Arthroscopic partial meniscectomy for degenerative meniscal tear. *N Engl J Med* 2014;370:1260.
28 Sadoghi P, Gomoll AH. New England journal of medicine article evaluating the usefulness of meniscectomy is flawed. *Arthroscopy* 2014;30:659–60.
29 Sihvonen R, Paavola M, Malmivaara A, *et al*. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. *N Engl J Med* 2013;369:2515–24.
30 Altman R, Asch E, Bloch D, *et al*. Development of criteria for the classification and reporting of osteoarthritis. classification of osteoarthritis of the knee. diagnostic and therapeutic Criteria Committee of the american Rheumatism Association. *Arthritis Rheum* 1986;29:1039–49.
31 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16:494–502.
32 Solomon DH, Simel DL, Bates DW, *et al*. The rational clinical examination. does this patient have a torn Meniscus or ligament of the knee? value of the physical examination. *JAMA* 2001;286:1610–20.
33 McMurray TP. The semilunar cartilages. *Br J Surg* 1942;29:407–14.
34 Sihvonen R, Paavola M, Malmivaara A, *et al*. Finnish degenerative meniscal lesion study (FIDELITY): a protocol for a randomised, placebo surgery controlled trial on the efficacy of arthroscopic partial meniscectomy for patients with degenerative Meniscus injury with a novel 'RCT within-a-cohort' study design. *BMJ Open* 2013;3:e002510.
35 Brittberg M, Winalski CS. Evaluation of cartilage injuries and repair. *J Bone Joint Surg Am* 2003;85-A(Suppl 2):58–69.
36 Anderson AF, Irrgang JJ, Dunn W, *et al*. Interobserver reliability of the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (ISAKOS) classification of meniscal tears. *Am J Sports Med* 2011;39:926–32.
37 Kirkley A, Griffin S, Whelan D. The development and validation of a quality of life-measurement tool for patients with meniscal pathology: the Western Ontario Meniscal Evaluation Tool (WOMET). *Clin J Sport Med* 2007;17:349–56.
38 Sihvonen R, Jarvela T, Aho H, *et al*. Validation of the Western Ontario Meniscal evaluation Tool (WOMET), a Meniscal pathology-specific Quality-of-Life index, for patients with a Degenerative Meniscus tear. *J Bone Joint Surg Am* 2012;94:e65–1-8.
39 Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res* 1985;198:43-9.
40 Briggs KK, Kocher MS, Rodkey WG, *et al*. Reliability, validity, and responsiveness of the Lysholm knee score and Tegner activity scale for patients with meniscal injury of the knee. *J Bone Joint Surg Am* 2006;88:698–705.
41 Hamilton DF, Lane JV, Gaston P, *et al*. What determines patient satisfaction with surgery? A prospective cohort study of 4709 patients following total joint replacement. *BMJ Open* 2013;3:e002525.
42 Dowrick AS, Bhandari M. Ethical issues in the design of randomized trials: to sham or not to sham. *J Bone Joint Surg Am* 2012;94(Suppl 1):7–10.
43 Kim JR, Kim BG, Kim JW, *et al*. Traumatic and non-traumatic isolated horizontal meniscal tears of the knee in patients less than 40 years of age. *Eur J Orthop Surg Traumatol* 2013;23:589–93.
44 Thorlund JB, Englund M, Christensen R, *et al*. Patient reported outcomes in patients undergoing arthroscopic partial meniscectomy for traumatic or degenerative meniscal tears: comparative prospective cohort study. *BMJ* 2017;356:j356.
45 Elattrache N, Lattermann C, Hannon M, *et al*. New England journal of medicine article evaluating the usefulness of meniscectomy is flawed. *Arthroscopy* 2014;30:542–3.
46 Rossi MJ, D'Agostino RB, Provencher MT, *et al*. Could the New England journal of medicine be biased against Arthroscopic knee surgery? *Arthroscopy* 2014;30:536–7.
47 Lyman S, Oh LS, Reinhardt KR, *et al*. Surgical decision making for arthroscopic partial meniscectomy in patients aged over 40 years. *Arthroscopy* 2012;28:492–501.
48 Englund M, Guermazi A, Roemer FW, *et al*. Meniscal tear in knees without surgery and the development of radiographic osteoarthritis among middle-aged and elderly persons: the Multicenter Osteoarthritis Study. *Arthritis Rheum* 2009;60:831–9.
49 Badlani JT, Borrero C, Golla S, *et al*. The effects of meniscus injury on the development of knee osteoarthritis: data from the osteoarthritis initiative. *Am J Sports Med* 2013;41:1238–44.
50 Dervin GF, Stiell IG, Wells GA, *et al*. Physicians' accuracy and interrator reliability for the diagnosis of unstable meniscal tears in patients having osteoarthritis of the knee. *Can J Surg* 2001;44:267–74.
51 Tornbjerg SM, Nissen N, Englund M, *et al*. Structural pathology is not related to patient-reported pain and function in patients undergoing meniscal surgery. *Br J Sports Med* 2017;51:525–30.
52 Englund M, Niu J, Guermazi A, *et al*. Effect of meniscal damage on the development of frequent knee pain, aching, or stiffness. *Arthritis Rheum* 2007;56:4048–54.
53 Sun X, Ioannidis JP, Agoritsas T, *et al*. How to use a subgroup analysis: users' guide to the medical literature. *JAMA* 2014;311:405–11.
54 Conaghan PG, Dickson J, Grant RL, *et al*. Care and management of osteoarthritis in adults: summary of NICE guidance. *BMJ* 2008;336:502–3.
55 Zhang W, Moskowitz RW, Nuki G, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage* 2007;15:981–1000.
56 Krych AJ, Stuart MJ, Levy BA. Arthroscopic partial meniscectomy for degenerative meniscal tear. *N Engl J Med* 2014;370:1259.
57 Yim JH, Seon JK, Song EK, *et al*. A comparative study of meniscectomy and nonoperative treatment for degenerative horizontal tears of the medial meniscus. *Am J Sports Med* 2013;41:1565–70.
58 Kise NJ, Risberg MA, Stensrud S, *et al*. Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up. *BMJ* 2016;354:i3740.
59 NICE. *Osteoarthritis: care and Management in adults*. London: National Institute for Health and Care Excellence (UK), 2014.
60 Sihvonen R, Englund M, Turkiewicz A, *et al*. Mechanical symptoms and arthroscopic partial meniscectomy in patients with degenerative Meniscus tear: a secondary analysis of a Randomized Trial. *Ann Intern Med* 2016;164:449–55.
61 Kirkley A, Birmingham TB, Litchfield RB, *et al*. A randomized trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2008;359:1097–107.
62 Sihvonen R, Englund M, Turkiewicz A, *et al*. Mechanical symptoms as an indication for knee arthroscopy in patients with degenerative Meniscus tear: a prospective cohort study. *Osteoarthritis Cartilage* 2016;24:1367–75.
63 Richmond JC. Surgery for osteoarthritis of the knee. *Rheum Dis Clin North Am* 2013;39:203–11.
64 Scillia AJ, McDermott JD, Issa K, *et al*. Arthroscopic partial meniscectomy for Meniscal Tears: a review and commentary on a study by NEJM. *J Knee Surg* 2016;29:387–90.
65 Roos EM, Thorlund JB. It is time to stop meniscectomy. *Br J Sports Med* 2017;51:490–1.

EXTENDED REPORT

Cigarette smoking and the risk of systemic lupus erythematosus, overall and by anti-double stranded DNA antibody subtype, in the Nurses' Health Study cohorts

Medha Barbhaiya, Sara K Tedeschi, Bing Lu, Susan Malspeis, David Kreps, Jeffrey A Sparks, Elizabeth W Karlson, Karen H Costenbader

Handling editor Tore K Kvien

Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

Correspondence to
Dr Medha Barbhaiya, Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, 60 Fenwood Road, Boston, MA 02115, USA;
barbhaiyam@hss.edu

Received 19 April 2017
Revised 31 July 2017
Accepted 15 September 2017
Published Online First
7 October 2017

ABSTRACT

Objectives Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease, subtyped according to clinical manifestations and autoantibodies. Evidence concerning cigarette smoking and SLE risk has been conflicting. We investigated smoking and SLE risk, overall and by anti-double stranded DNA (dsDNA) presence, in two prospective cohort studies.

Methods The Nurses' Health Study (NHS) enrolled 121 701 US female nurses in 1976; Nurses' Health Study II (NHSII) enrolled 116 430 in 1989. Lifestyle, environmental and medical data were collected through biennial questionnaires. Incident SLE was confirmed by medical record review. Cox regression models estimated HRs of SLE, overall and by dsDNA subtype, in association with time-varying smoking status and cumulative smoking pack-years through the 2-year cycle prior to diagnosis, controlling for potential confounders.

Results Among 286 SLE cases identified (159 in NHS (1978–2012) and 127 in NHSII (1991–2013)), mean age was 49.2 (10.3) years and 42% were dsDNA+ at SLE diagnosis. At baseline, 45% of women had ever smoked, 51% of whom currently smoked. Compared with never smokers, current smokers had increased dsDNA+ SLE risk (HR 1.86 (1.14–3.04)), whereas past smokers did not (HR 1.31 (0.85–2.00)). Women who smoked >10 pack-years (vs never) had an elevated dsDNA+ SLE risk (HR 1.60(95% CI 1.04 to 2.45)) compared with never smokers. No associations were observed between smoking status or pack-years and overall SLE or dsDNA– SLE.

Conclusion Strong and specific associations of current smoking and >10 pack-years of smoking with dsDNA+ SLE were observed. This novel finding suggests smoking is involved in dsDNA+ SLE pathogenesis.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease with subtypes defined by autoantibodies and clinical manifestations. Anti-double stranded DNA (dsDNA) antibodies are specific for SLE, involved in lupus nephritis pathogenesis and disease activity biomarkers.[1–4] Patients with the dsDNA positive (dsDNA+) subtype have increased risk for a more aggressive disease course, particularly with lupus nephritis and vasculitis.

SLE pathogenesis involves both genetic and environmental factors.[5] Past studies suggest smoking is related to increased SLE risk, although results are conflicting, with two prior null prospective cohort studies.[6–10] In a SLE case-only study, current smokers were more likely than never smokers to have dsDNA antibodies (OR 4.0 (95% CI 1.6 to 10.4)).[11]

We investigated smoking and risk of developing SLE and SLE subtypes according to dsDNA status among women. We hypothesised that current smokers compared with never smokers would have an increased risk of overall and dsDNA+ SLE. We evaluated smoking and other SLE-related antibody subtypes characterised by anti-Ro and/or anti-La (Ro/La), or anti-Smith (Sm) antibodies. To our knowledge, no prior study has prospectively investigated smoking and risk of incident SLE stratified by autoantibody status.

PATIENTS AND METHODS

Study population

The Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) are prospective cohorts of registered female nurses who completed a baseline and biennial questionnaires on risk factors, lifestyle, health practices and diagnoses. In 1976, NHS enrolled 121 700 nurses aged 30–55 years from 11 US states. In 1989, NHSII enrolled 116 670 nurses aged 25–42 years from 14 states. Both cohorts are predominantly White (>90%), with >90% response rates to follow-up questionnaires and 5.0% of person-time lost to follow-up.[12] Deaths are reported by family members and ascertained via National Death Index searches, with cause of death validated by medical record review.

We excluded participants who reported prevalent SLE or other connective tissue diseases (CTD) and those without smoking information on baseline questionnaires. After exclusions, 117 157 NHS participants and 113 527 NHSII participants were included.

Identification of incident SLE

SLE self-reports were confirmed by CTD screening questionnaire and medical record review by two independent rheumatologists.[13 14] SLE cases fulfilled at least four American College of Rheumatology 1997 SLE classification criteria on medical record review.[15 16] Anti-dsDNA, Sm,

To cite: Barbhaiya M, Tedeschi SK, Lu B, *et al*. *Ann Rheum Dis* 2018;**77**:196–202.

Ro, La status at SLE diagnosis was determined by medical record review.

The primary outcome was SLE, overall and by dsDNA status (including dsDNA+ or dsDNA− (dsDNA negative) SLE). As secondary outcomes, we stratified by other SLE-related antibody subtypes including: (1) dsDNA and/or Sm positive (dsDNA+/Sm+) versus dsDNA and Sm negative (dsDNA− and Sm−) SLE, (2) Ro and/or La positive (Ro+/La+) versus Ro and La negative (Ro− and La−) SLE, and (3) positivity for any SLE-related antibody (dsDNA+/Sm+/Ro+/La+ SLE) versus none of these. Too few SLE cases had only anti-Ro, La, Sm or ribonucleoprotein (RNP) at diagnosis for separate analyses.

Smoking exposure

At baseline, participants reported smoking status (never/past/current) and age of smoking initiation. Current smokers provided number of cigarettes smoked per day, whereas past smokers reported age at quitting smoking and cigarettes/day before quitting. On subsequent questionnaires, participants reported smoking status and smoking intensity (1–4, 5–14, 15–24, 25–34 or 35–44 cigarettes/day). Smoking pack-years were derived by multiplying packs per day (20 cigarettes per pack) with years smoked. All smoking variables were time varying, updated every 2 years, as smokers often stop and restart.

Assessment of covariates

Sociodemographic data included age, race/ethnicity and US Census tract-based median household income as a measure of area socioeconomic status. Updated body mass index (BMI) was reported and caloric intake was calculated from a semiquantitative food frequency questionnaire.[17] Alcohol consumption was categorised as never, >0 to <5 g/day, ≥5 g/day as in a previous analysis.[18] Reproductive covariates, including oral contraceptive use, menarche onset age, menopausal status and postmenopausal hormone use, were examined as potential confounders.[13] Missing covariate data were carried forward one cycle and if missing beyond one cycle, we included a missing data variable category.

Statistical analysis

In our primary analyses, we assessed the association between time-varying smoking status and SLE risk, overall and by dsDNA subtypes, through the 2-year cycle prior to SLE diagnosis. Person-years of follow-up accrued from return of baseline questionnaire until the 2-year cycle prior to SLE diagnosis, end of follow-up, death or date of censor, whichever came first. Participants were censored for self-reported CTD (SLE, rheumatoid arthritis (RA), scleroderma, Sjögren's syndrome, mixed CTD or inflammatory myositis) not confirmed as SLE. We carried forward the last observation up to two questionnaire cycles for missing smoking status or duration.

We examined baseline characteristics across smoking status categories by cohort. We determined cut-points for categories of continuous exposure variables non-parametrically with restricted cubic splines.[19] We used Cox proportional hazards models to assess the HRs and 95% CI for smoking status and overall SLE, dsDNA+ and dsDNA− SLE in separate models, controlling for time-varying covariates. We constructed three models for each endpoint: (1) age and questionnaire period adjusted; (2) additional adjustment for alcohol; and (3) additional adjustment for race, socioeconomic status and reproductive factors. Based on the generalised Wald test for a joint hypothesis on all covariate–time interactions in the models, the proportional hazards assumption was not violated. NHS and NHSII data were pooled. In a sensitivity analysis to evaluate the robustness of pooling the data, HR estimates from the two cohorts were meta-analysed using a fixed effects model.

We conducted several secondary analyses. First, we investigated cumulative smoking in pack-years and risk of SLE and dsDNA subtypes. Second, we cross-classified smoking status and pack-years and examined SLE risk overall and by dsDNA. Third, we separately evaluated the associations of smoking intensity (collapsed to >0 to <15 or ≥15 cigarettes/day) and duration (≥20 years or <20 years) with SLE risk. Fourth, we conducted a 'lagged analysis' in which the exposure window ended two questionnaire cycles (at least 4 years) prior to the outcome window, as SLE may develop insidiously prediagnosis and illness could change smoking behaviour. Fifth, we examined smoking cessation. Lastly, we investigated the association between time-varying smoking and SLE with other autoantibody subtypes.

Data analyses were performed using SAS V.9.3 (SAS Institute). The Partners' HealthCare Institutional Review Board approved all aspects of this study.

RESULTS

Among 230 672 women with 5.6 million person-years of follow-up, we identified 286 incident SLE cases: 159 SLE cases in NHS and 127 in NHSII. Average annual SLE incidence rates in each cohort were 4.9 per 100 000 person-years for NHS and 5.3 per 100 000 person-years for NHSII, as expected for predominantly White women aged ≥25 years at cohort entry. At baseline, 45% of women in both cohorts were ever smokers, of whom 51% were current smokers. Table 1 displays age-adjusted baseline characteristics of study participants categorised by smoking status. Age, race, caloric intake, BMI, postmenopausal status, postmenopausal hormone use and early menarche were similar across smoking categories within each cohort. Alcohol consumption was higher among smokers than non-smokers. Most current smokers had smoked >10 pack-years, although women in NHS were heavier smokers than those in NHSII.

The presenting manifestations at SLE diagnosis, overall and by dsDNA subtype, are shown in table 2. Of the 286 incident SLE cases, 42% were dsDNA+ at diagnosis. Mean age at SLE diagnosis was 49.2 years (SD 10.3). There were more non-Whites in the dsDNA+ (12.6%) versus dsDNA− (6.1%) subgroup. Among women with dsDNA+ SLE, there were lower rates of arthritis (65.3% vs 79.4%), higher rates of haematological involvement (65.3% vs 53.3%) and similar rates of renal involvement (16.5% vs 16.4%) compared with dsDNA− SLE in records reviewed around the time of SLE diagnosis.

Among SLE cases, the largest proportion of past and current smokers smoked 15–24 cigarettes/day (34.4% and 37.5%). Mean smoking duration among SLE cases was greater for current than past smokers (26.4 (SD 8.9) vs 16.1 (SD 10.8) years). Among SLE cases, mean time since quitting among past smokers was 16.8 (SD 12.8) years. The mean age at SLE diagnosis was similar between dsDNA+ SLE (51.0 (SD 10.0) years) compared with dsDNA− SLE (50.9 (SD 11.3) years), yielding a nearly identical interval between age at smoking initiation among SLE ever-smokers (18.4 (SD 3.7) years) and age at SLE diagnosis for dsDNA+ and dsDNA− SLE cases.

No significant risk was observed among past or current smokers (vs never smokers) for SLE overall or dsDNA− SLE risk (table 3). However, current smoking was associated with a strongly increased risk of dsDNA+ SLE after age and sex adjustment (HR 1.77 (95% CI 1.09 to 2.88)) and additional

Table 1 Baseline age-standardised characteristics of participants in the Nurses' Health Study (NHS) in 1976 and Nurses' Health Study II (NHSII) in 1989 categorised by smoking status

	NHS (n=117 145)			NHSII (n=113 527)		
Characteristics	**Never**	**Past**	**Current**	**Never**	**Past**	**Current**
Number of participants (%)	51 655 (44.1)	26 889 (23.0)	38 601 (33.0)	74 166 (65.3)	24 152 (21.3)	15 209 (13.4)
Mean age in years (SD)*	42.4 (7.4)	42.6 (7.1)	42.4 (7.1)	34.0 (4.7)	35.2 (4.5)	34.8 (4.6)
White race (%)	92	94	94	91	94	93
Median income ≥$60 000 (%)†	46	53	49	43	50	40
Mean calorie intake (kcal/day, SD)	1588 (502)	1553 (488)	1546 (510)	1799 (547)	1783 (542)	1753 (559)
Mean body mass index (kg/m^2, SD)	24.1 (4.3)	23.9 (4.3)	23.2 (3.9)	24.1 (5.1)	24.1 (5.0)	24.1 (5.0)
Smoking in pack-year categories						
0 (%)	100	0	0	100	0	0
>0 to ≤10 (%)	0	58	20	0	69	36
>10 (%)	0	42	80	0	31	64
Oral contraceptive use, ever (%)	45	49	49	81	89	89
Postmenopausal (%)	31	30	34	6	6	8
Any postmenopausal hormone use (%)	13	14	15	3	3	4
Early menarche (≤10 years) (%)	6	6	6	8	8	9
Alcohol use in categories (g/day) (%)‡						
None	33	19	19	43	28	28
>0 to <5	27	27	24	42	43	40
≥5	19	34	32	15	28	32

Means (SD) or percentages, age standardised to distribution of study population.
*Not age standardised.
†Zip code-level median household income from the US Census.
‡Cumulative average daily alcohol consumption.
g/day, grams per day; kcal/day, kilocalories per day.

adjustment for alcohol use (HR 1.91 (95% CI 1.17 to 3.12)). This risk remained significant in the multivariable (MV) model (HR 1.86 (95% CI 1.14 to 3.04)). Meta-analysing HRs from the two cohorts produced similar results for current versus never smoking (MV-adjusted HR for dsDNA+ SLE 1.81 (95% CI 1.10 to 2.96), Q value=0.01 with p=0.94, Tau^2=0), and no association with overall SLE or dsDNA− SLE. In a 'lagged' analysis allowing 4 years before SLE diagnosis, the risk of dsDNA+ SLE was potentially even more elevated among current versus never smokers (MV-adjusted HR 1.93 (95% CI 1.17 to 3.18)).

In secondary analyses, we examined smoking in pack-years (table 4). Based on the results of the restricted cubic splines, we defined pack-years using an ordinal variable (0 pack-years, >0 to ≤10 pack-years, >10 pack-years). Although no significant association for smoking in pack-years and risk of overall SLE or dsDNA− SLE was demonstrated, women who smoked >10 pack-years had a significantly elevated risk of dsDNA+ SLE (HR 1.60 (95% CI 1.04 to 2.45), p trend 0.04) compared with never smokers. In an analysis cross-classifying smoking status with pack-years, current smokers who smoked >10 pack-years had a potential 67% increased risk of dsDNA+ SLE (HR 1.67 (95% CI 0.98 to 2.85), p trend 0.07 across pack-year categories), but no increased risk of SLE overall (HR 1.05 (95% CI 0.72 to 1.51), p trend 0.81). No association was demonstrated between increased pack-years and all SLE or dsDNA+ SLE among past smokers.

Among current smokers, increasing smoking intensity (≥15 vs >0 to <15 cigarettes/day) was not associated with increased dsDNA+ SLE risk after MV adjustment (p=0.38). However, among current smokers, increasing smoking duration was related to increased dsDNA+ SLE risk (MV HR 1.85 (95% CI 1.09 to 3.13)) for those continuing to smoke for ≥20 years compared with never smokers. No association was demonstrated for increasing smoking duration and overall or dsDNA− SLE, or among past smokers.

Among past smokers, no association between time since quitting and risk of SLE or dsDNA− SLE was found. However, after quitting smoking for >5 years, the risk of dsDNA+ SLE was no longer significantly elevated (HR 1.11 (95% CI 0.69 to 1.79) vs never smokers), demonstrating a significant threshold in risk reduction at >5 years (figure 1).

Current smoking, but not past smoking (compared with never smoking), was associated with a significantly increased risk of dsDNA+/Sm+ SLE (HR 1.87 (95% CI 1.14 to 3.06)) and dsDNA+/Sm+/Ro+/La+ SLE (HR 1.84 (95% CI 1.15 to 2.93)). However, no association was demonstrated between current or past smoking (vs never smoking) and other SLE subtypes identified by autoantibody profiles (table 5).

Table 2 Characteristics of participants at SLE diagnosis in Nurses' Health Study and Nurses' Health Study II by anti-double stranded DNA (dsDNA) antibody status

Characteristics at SLE diagnosis	**Overall SLE (n=286)**	**dsDNA+ SLE (n=121)**	**dsDNA− SLE (n=165)**
Mean age at diagnosis, years (SD)	49.2 (10.3)	49.9 (9.6)	48.7 (10.8)
White race (%)	91.6	88.4	93.9
Antinuclear antibody positive (%)	97.6	98.4	97.0
Arthritis (%)	73.4	65.3	79.4
Haematological involvement (%)	58.4	65.3	53.3
Renal involvement (%)	16.4	16.5	16.4
Mean number of ACR SLE criteria met (SD)	4.9 (1.1)	5.2 (1.2)	4.7 (0.9)
Diagnosed by ACR member rheumatologist (%)	79.0	76.0	81.2

ACR, American College of Rheumatology; dsDNA+, double stranded DNA positive; dsDNA−, double stranded DNA negative; SLE, systemic lupus erythematosus.

Table 3 Association between cigarette smoking status and risk of incident SLE among participants in Nurses' Health Study and Nurses' Health Study II, overall and by anti-double stranded DNA (dsDNA) antibody status

	Cigarette smoking status		
	Never	Past	Current
Overall SLE			
Cases/person-years	148/3 074 178	90/1 759 984	48/808 162
Age-adjusted HR (95% CI)*	1.00 (ref)	1.12 (0.86 to 1.47)	1.07 (0.77 to 1.50)
Alcohol-adjusted HR (95% CI)†	1.00 (ref)	1.22 (0.93 to 1.60)	1.17 (0.8 to 1.65)
Multivariable-adjusted HR (95% CI)‡	1.00 (ref)	1.18 (0.89 to 1.55)	1.14 (0.81 to 1.61)
dsDNA+ SLE			
Cases/person-years	56/3 073 263	39/1 759 395	26/807 828
Age-adjusted HR (95% CI)*	1.00 (ref)	1.29 (0.85 to 1.95)	**1.77 (1.09 to 2.88)**
Alcohol-adjusted HR (95% CI)†	1.00 (ref)	1.37 (0.89 to 2.09)	**1.91 (1.17 to 3.12)**
Multivariable-adjusted HR (95% CI)‡	1.00 (ref)	1.31 (0.85 to 2.00)	**1.86 (1.14 to 3.04)**
dsDNA– SLE			
Cases/person-years	92/3 073 468	51/1 759 406	22/807 827
Age-adjusted HR (95% CI)*	1.00 (ref)	1.02 (0.72 to 1.45)	0.72 (0.44 to 1.16)
Alcohol-adjusted HR (95% CI)†	1.00 (ref)	1.13 (0.79 to 1.61)	0.79 (0.49 to 1.29)
Multivariable-adjusted HR (95% CI)‡	1.00 (ref)	1.09 (0.76 to 1.56)	0.76 (0.47 to 1.24)

p for heterogeneity between the cohorts >0.05 for all analyses.
*Adjusted for age (months), questionnaire cycle, cohort.
†Additionally adjusted for alcohol intake (never, >0 to <5 g/day, ≥5 g/day).
‡Additionally adjusted for race (White vs non-White), body mass index in WHO categories (18.5 to <25, 25 to <30, ≥30), zip code-level median household income from US Census (≥60 000 vs <60 000), oral contraceptive use (ever/never), age at menarche (≤10 vs >10 years), menopausal status and postmenopause hormone (PMH) use (premenopausal, postmenopausal/never used PMH, postmenopausal/ever used PMH).
Bold numbers meet statistical significance threshold of p<0.05.
dsDNA+, double stranded DNA positive; dsDNA–, double stranded DNA negative; SLE, systemic lupus erythematosus; WHO, World Health Organization.

DISCUSSION

In these large prospective cohorts of women followed for many years prior to SLE onset, we found a strong and specific association between smoking and dsDNA+ SLE. While no association was seen between smoking and risk of overall SLE, dsDNA+ SLE risk was increased nearly twofold among current smokers and by 60% among women who smoked >10 pack-years, compared with never smokers. Risks of dsDNA+/Sm+ and dsDNA+/Sm+/Ro+/La+ SLE were similarly elevated among current smokers. Among current smokers, dsDNA+ SLE risk was nearly doubled after smoking ≥20 years and we found a significant reduction in dsDNA+ SLE risk after quitting smoking

Table 4 Association between cigarette smoking in pack-years and risk of incident SLE among participants in Nurses' Health Study and Nurses' Health Study II, overall and by anti-double stranded DNA (dsDNA) antibody status

	Pack-years			
	Never smoker	>0 to ≤10	>10	p Trend
Overall SLE				
Cases/person-years	148/3 074 178	52/1 032 876	86/1 535 233	
Age-adjusted HR (95% CI)*	1.00 (ref)	1.03 (0.75 to 1.41)	1.16 (0.88 to 1.54)	0.28
Alcohol-adjusted HR (95% CI)†	1.00 (ref)	1.11 (0.81 to 1.54)	1.27 (0.96 to 1.68)	0.10
Multivariable-adjusted HR (95% CI)‡	1.00 (ref)	1.09 (0.79 to 1.51)	1.22 (0.92 to 1.61)	0.18
dsDNA+ SLE				
Cases/person-years	56/3 073 263	24/1 032 491	41/1 534 731	
Age-adjusted HR (95% CI)*	1.00 (ref)	1.27 (0.78 to 2.05)	**1.57 (1.04 to 2.39)**	**0.04**
Alcohol-adjusted HR (95% CI)†	1.00 (ref)	1.35 (0.83 to 2.20)	**1.68 (1.10 to 2.58)**	**0.02**
Multivariable-adjusted HR (95% CI)‡	1.00 (ref)	1.32 (0.81 to 2.16)	**1.60 (1.04 to 2.45)**	**0.04**
dsDNA– SLE				
Cases/person-years	92/3 073 468	28/1 032 494	45/1 534 739	
Age-adjusted HR (95% CI)*	1.00 (ref)	0.88 (0.57 to 1.35)	0.93 (0.64 to 1.35)	0.75
Alcohol-adjusted HR (95% CI)†	1.00 (ref)	0.97 (0.63 to 1.49)	1.03 (0.70 to 1.50)	0.87
Multivariable-adjusted HR (95% CI)‡	1.00 (ref)	0.94 (0.61 to 1.46)	0.98 (0.67 to 1.44)	0.96

p for heterogeneity between the cohorts >0.05 for all analyses.
*Adjusted for age (months), questionnaire cycle, cohort.
†Additionally adjusted for alcohol intake (never, >0 to <5 g/day, ≥5 g/day).
‡Additionally adjusted for race (White vs non-White), body mass index in WHO categories (18.5 to <25, 25 to <30, ≥30), zip code-level median household income from US Census (≥60 000 vs <60 000), oral contraceptive use (ever/never), age at menarche (≤10 vs >10 years), menopausal status and postmenopause hormone (PMH) use (premenopausal, postmenopausal/never used PMH, postmenopausal/ever used PMH).
Bold numbers meet statistical significance threshold of p<0.05.
dsDNA+, double stranded DNA positive; dsDNA–, double stranded DNA negative; SLE, systemic lupus erythematosus; WHO, World Health Organization.

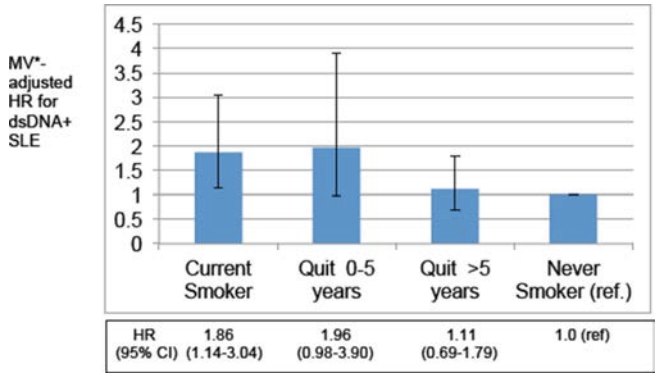


Figure 1 Association of smoking cessation and risk of anti-double stranded DNA positive (dsDNA+) SLE among participants in Nurses' Health Study and Nurses' Health Study II. p for heterogeneity between the cohorts >0.05 for all analyses. *Adjusted for age (months), questionnaire cycle, cohort, alcohol intake (never, >0 to <5 g/day, ≥5 g/day), race (White vs. non-White), body mass index in WHO categories (18.5 to <25, 25 to <30, ≥30) , zip code-level median household income from U.S. census (≥60,000 versus <60,000), oral contraceptive use (ever/never), age at menarche (≤10 vs. >10 years), menopausal status and post-menopause hormone (PMH) use (pre-menopausal, post-menopausal/never used PMH, post-menopausal/ever used PMH). CI, confidence interval; HR, hazard ratio; MV, multivariable; SLE, systemic lupus erythematosus.

for >5 years. Thus, we found positive short-term risk using time-varying updated smoking status and long-term risk using cumulative cigarette smoking in pack-years over up to 37 years. This is the largest and longest prospective study to investigate SLE risk using repeated measures of smoking exposure. These studies newly describe a specific association between current smoking and the subtype of SLE characterised by dsDNA antibodies.

Our findings are consistent with and extend prior studies. Although epidemiologic studies of smoking and SLE risk have been somewhat conflicting,[8 20 21] our earlier meta-analysis of seven case–control and two cohort studies demonstrated elevated SLE risk among current smokers (OR 1.5, 95% CI 1.09 to 2.08) compared with non-smokers, but not past smokers (OR 0.98, 95% CI 0.75 to 1.27).[22] Since then, additional case–control studies have demonstrated an elevated SLE risk among smokers compared with never smokers.[6–8 23] Prior studies included heterogeneous groups with varying race/ethnicities—with no association for smoking and SLE among black women,[10] a significantly increased risk among predominantly Hispanic smokers[20] and varied risks among Asian subgroups.[6 8]

Several case–control studies have reported dose–response relationships for SLE risk with increasing pack-years.[8 21 24] Two past prospective cohort studies, the NHS (1996) and the Black Women's Health Study (BWHS, 2003), did not demonstrate significant associations between smoking and SLE risk.[9 10] Both cohorts were limited at the time by small sample size, one-time baseline assessment of exposure in BWHS and short exposure duration.

In a recent case–control study, current smoking was associated with presence of ≥1 SLE-related autoantibody (OR 1.53 (95% CI 1.04 to 2.24)) and an increased rate of anti-RNP A positivity among patients with SLE, whereas former smoking was associated with increased risk of anti-Ro positivity among unaffected first-degree relatives.[25] Although our study was underpowered to evaluate the risk of all SLE-related antibody subtypes individually, our results demonstrate a strong association between current smoking and dsDNA+/Sm+ and dsDNA+/Sm+/Ro+/La+ SLE subtypes. Anti-dsDNA+ SLE may also be a more homogeneous and severe phenotype than dsDNA− SLE, possibly explaining the stronger association with smoking.

Epidemiologic evidence suggests that tobacco smoke exposure is associated with other autoimmune diseases such as RA, Graves' disease and primary biliary cirrhosis.[26–30] Notably, our findings parallel RA studies demonstrating an association between smoking and increased risk of seropositive RA (with rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies), but not seronegative RA.[29 31] We have previously demonstrated increased risk of seropositive RA among both current (relative risk (RR) 1.58 (1.21–2.06)) and past smokers (RR 1.60 (1.27–2.02)), and with ≥10 pack-years of smoking, as well as with increased smoking duration and intensity compared with never smokers.[29] However, whereas RA risk remained elevated until 20 years after smoking cessation,[29] here we find dsDNA+ SLE risk was reduced after >5 years of smoking cessation.

Our results suggest a biological role for smoking in the development of dsDNA+ SLE, although the mechanistic basis is not yet understood. Exposures to toxic components from cigarette smoke (eg, tars, nicotine, carbon monoxide, polycyclic aromatic hydrocarbons and free radicals) induce oxidative stress, damage endogenous proteins and DNA, and lead to genetic mutations and gene activation.[32] Toxic smoke components also induce epigenetic changes, resulting in altered gene expression affecting immunity[33 34] and production of proinflammatory cytokines including tumour necrosis factor-α and interleukin-6.[35 36] Smoking also stimulates surface expression of CD95 on B and CD4+ T cells, potentially leading to ineffective clearing of apoptotic neutrophils and dsDNA autoantibody production.[37 39] Reactive oxygen species from tobacco damage DNA, forming immunogenic DNA adducts, which may result in dsDNA antibody production.[26 27] As in many tobacco-induced complex diseases, genetic background likely plays a role in whether a smoker will develop dsDNA antibodies and SLE. In a past case–control study, the cytochrome P450 1A1 rs4646903 and glutathione S-transferase M1 deletion genotypes, both involved in detoxification pathways, were associated with greatly increased SLE risk among smokers (OR 17.5 (95% CI 3.20 to 95.9)).[40] Our study was not designed to investigate disease mechanisms, and future research investigating gene–environment interactions and epigenetic modifications is warranted.

A major strength of the current study is the use of two large cohorts with over 5.6 million person-years of prospective follow-up. Detailed exposure data updated every 2 years allowed for evaluation of smoking status, cumulative smoking in pack-years, duration, intensity and time since quitting, enhancing precision and reducing the likelihood of misclassification of exposure, within-subject variation and recall biases. Autoantibody status was assessed at SLE diagnosis, minimising the possibility that SLE-specific antibodies may have normalised after drug treatment. Furthermore, our 'lagged' analysis demonstrated a potentially greater risk of current smoking for incident dsDNA+ SLE, suggesting that smokers may quit in the years immediately preceding SLE diagnosis. Our stringent method for SLE classification along with identification of SLE-associated antibodies increased the likelihood that identified cases were truly SLE.

Given our stringent definition of SLE, we may have excluded possible SLE cases upon medical record review that later may have become more clinically apparent. As we assessed dsDNA, Sm, Ro, La seropositivity at SLE diagnosis, cases that later developed these antibodies may have been misclassified as being negative. However, given that SLE-related antibodies become

Table 5 Association between cigarette smoking status and risk of incident systemic lupus erythematosus (SLE) among participants in Nurses' Health Study and Nurses' Health Study II, overall and by SLE autoantibody subtypes

	Cigarette smoking status		
	Never	Past	Current
dsDNA+/Sm+ SLE			
Cases/person-years	56/3 073 179	40/1 759 315	26/807 775
Age-adjusted HR (95% CI)*	1.00 (ref)	1.31 (0.87 to 1.98)	**1.77 (1.09 to 2.88)**
Multivariable-adjusted HR (95% CI)†	1.00 (ref)	1.33 (0.87 to 2.03)	**1.87 (1.14 to 3.06)**
dsDNA– and Sm– SLE			
Cases/person-years	92/3 073 375	50/1 759 273	22/807 765
Age-adjusted HR (95% CI)*	1.00 (ref)	1.00 (0.71 to 1.43)	0.72 (0.44 to 1.16)
Multivariable-adjusted HR (95% CI)†	1.00 (ref)	1.07 (0.75 to 1.54)	0.76 (0.47 to 1.24)
Ro+/La+ SLE			
Cases/person-years	19/3 072 720	15/1 759 053	3/807 523
Age-adjusted HR (95% CI)*	1.00 (ref)	1.37 (0.68 to 2.75)	0.85 (0.25 to 2.94)
Multivariable-adjusted HR (95% CI)†	1.00 (ref)	1.42 (0.69 to 2.91)	0.85 (0.25 to 2.94)
Ro– and La– SLE			
Cases/person-years	129/3 073 859	75/1 759 629	45/808 032
Age-adjusted HR (95% CI)*	1.00 (ref)	1.08 (0.81 to 1.45)	1.09 (0.77 to 1.55)
Multivariable-adjusted HR (95% CI)†	1.00 (ref)	1.14 (0.85 to 1.54)	1.18 (0.82 to 1.68)
dsDNA+/Sm+/Ro+/La+ SLE			
Cases/person-years	63/3 073 307	48/1 759 419	28/807 833
Age-adjusted HR (95% CI)*	1.00 (ref)	1.39 (0.94 to 2.03)	**1.75 (1.10 to 2.78)**
Multivariable-adjusted HR (95% CI)†	1.00 (ref)	1.41 (0.95 to 2.09)	**1.84 (1.15 to 2.93)**
dsDNA– and Sm– and Ro– and La– SLE			
Cases/person-years	85/3 073 202	42/1 759 200	20/807 715
Age-adjusted HR (95% CI)*	1.00 (ref)	0.92 (0.63 to 1.35)	0.67 (0.41 to 1.11)
Multivariable-adjusted HR (95% CI)†	1.00 (ref)	0.99 (0.67 to 1.45)	0.72 (0.43 to 1.20)

p for heterogeneity between the cohorts >0.05 for all analyses.
*Adjusted for age (months), questionnaire cycle, cohort.
†Additionally adjusted for alcohol intake (never, >0 to <5 g/day, ≥5 g/day), race (White vs non-White), body mass index in WHO categories (18.5 to <25, 25 to <30, ≥30) , zip code-level median household income from US Census (≥60 000 vs <60 000), oral contraceptive use (ever/never), age at menarche (≤10 vs >10 years), menopausal status and postmenopause hormone (PMH) use (premenopausal, postmenopausal/never used PMH, postmenopausal/ever used PMH).
Bold numbers meet statistical significance threshold of p<0.05.
dsDNA, anti-double stranded DNA antibodies; dsDNA+/Sm+, dsDNA and/or Sm positive; dsDNA+/Sm+/Ro+/La+, dsDNA and/or Sm and/or Ro and/or La positive; dsDNA–/Sm–/Ro–/La–, dsDNA and Sm and Ro and La negative; dsDNA– and Sm–, dsDNA and Sm negative; La, anti-La antibodies; Ro, anti-Ro antibodies; Ro+/La+, Ro and/or La positive; Ro– and La–, Ro and La negative; Sm, anti-Smith antibodies; WHO, World Health Organization.

positive years before diagnosis,[41] this misclassification was likely uncommon. Furthermore, as NHS/NHSII enrolled women between the ages of 25 and 55, our study may not have captured early-onset SLE. Additionally, given that the NHS cohorts include mostly healthy, White US women working in advanced nursing professions, there is a potential lack of generalisability to younger women, men and non-Whites. It is not known whether the association between smoking and dsDNA+ SLE may vary by sex, age or race/ethnicity.[20]

This study demonstrates a strong and specific association between current smoking and risk of dsDNA+ SLE, a severe subtype of SLE. Current smoking and smoking >10 pack-years were associated with increased risk of dsDNA+ SLE, and SLE subtypes characterised by dsDNA+/Sm+ or dsDNA+/Sm+/Ro+/La+. Further studies may be able to assess the association between smoking and SLE with individual autoantibodies, although this may be challenging as they are highly intercorrelated. Smoking cessation was shown to reduce dsDNA+ SLE risk to that of non-smokers after 5 years, suggesting that dsDNA+ SLE risk is modifiable. These findings have implications for SLE prevention efforts using personalised strategies for risk stratification and modification. They also demonstrate the importance of studying specific SLE subtypes and provide insight into potential mechanisms of disease pathogenesis warranting further research.

Acknowledgements We thank the participants in the NHS and NHSII cohorts for their dedication and continued participation in these longitudinal studies, as well as the NHS staff in the Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School for their assistance with this project.

Contributors MB and KHC designed the study, analysed the data and wrote the first draft. SM and BL contributed to the data analysis. MB, SKT, SM, DK, JAS, EWK and KHC were involved in data collection. All authors were involved in drafting the article and revising it critically for important intellectual content, and all authors approved the final version to be published. MB and KHC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding Research reported in this publication was supported by the National Institutes of Health (NIH) grants AR049880, AR047782, AR066109, AR066953, AR070514, AR069688, CA186107, CA176726, CA49449 and CA67262. MB and JAS are both supported by the Rheumatology Research Foundation Scientist Development Awards. SKT is supported by the Lupus Foundation of America Career Development Award. The funders had no role in study design, data collection, analysis, decision to publish or preparation of the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the views of the National Institutes of Health.

Competing interests None declared.

Ethics approval Partners HealthCare Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Yung S, Cheung KF, Zhang Q, *et al*. Anti-dsDNA antibodies bind to mesangial annexin II in lupus nephritis. *J Am Soc Nephrol* 2010;21:1912–27.
2 Sun KH, Yu CL, Tang SJ, *et al*. Monoclonal anti-double-stranded DNA autoantibody stimulates the expression and release of IL-1beta, IL-6, IL-8, IL-10 and TNF-alpha from normal human mononuclear cells involving in the lupus pathogenesis. *Immunology* 2000;99:352–60.
3 Zhang H, Fu R, Guo C, *et al*. Anti-dsDNA antibodies bind to TLR4 and activate NLRP3 inflammasome in lupus monocytes/macrophages. *J Transl Med* 2016;14:156.
4 Chen CY, Tseng HM, Chen LC, *et al*. Use of a new fluorescence immunoassay to detect anti-dsDNA antibodies is more correlated with disease activity and complement than the ELISA method in SLE patients. *Lupus* 2003;12:266–73.
5 Barbhaiya M, Costenbader KH. Environmental exposures and the development of systemic lupus erythematosus. *Curr Opin Rheumatol* 2016;28:497–505.
6 Washio M, Horiuchi T, Kiyohara C, *et al*. Smoking, drinking, sleeping habits, and other lifestyle factors and the risk of systemic lupus erythematosus in Japanese females: findings from the KYSS study. *Mod Rheumatol* 2006;16:143–50.
7 Ekblom-Kullberg S, Kautiainen H, Alha P, *et al*. Smoking and the risk of systemic lupus erythematosus. *Clin Rheumatol* 2013;32:1219–22.
8 Kiyohara C, Washio M, Horiuchi T, *et al*. Kyushu Sapporo SLE (KYSS) Study Group. Cigarette smoking, alcohol consumption, and risk of systemic lupus erythematosus: a case-control study in a Japanese population. *J Rheumatol* 2012;39:1363–70.
9 Sánchez-Guerrero J, Karlson EW, Colditz GA, *et al*. Hair dye use and the risk of developing systemic lupus erythematosus. *Arthritis Rheum* 1996;39:657–62.
10 Formica MK, Palmer JR, Rosenberg L, *et al*. Smoking, alcohol consumption, and risk of systemic lupus erythematosus in the Black Women's Health Study. *J Rheumatol* 2003;30:1222–6.
11 Freemer MM, King TE, Criswell LA. Association of smoking with dsDNA autoantibody production in systemic lupus erythematosus. *Ann Rheum Dis* 2006;65:581–4.
12 Chen WY, Rosner B, Hankinson SE, *et al*. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. *JAMA* 2011;306:1884–90.
13 Costenbader KH, Feskanich D, Stampfer MJ, *et al*. Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. *Arthritis Rheum* 2007;56:1251–62.
14 Karlson EW, Sanchez-Guerrero J, Wright EA, *et al*. A connective tissue disease screening questionnaire for population studies. *Ann Epidemiol* 1995;5:297–302.
15 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 19971725;40(9.
16 Tan EM, Cohen AS, Fries JF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–7.
17 Hu FB, Rimm E, Smith-Warner SA, *et al*. Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. *Am J Clin Nutr* 1999;69:243–9.
18 Barbhaiya M, Lu B, Sparks JA, *et al*. Influence of Alcohol Consumption on the Risk of Systemic Lupus Erythematosus Among Women in the Nurses' Health Study Cohorts. *Arthritis Care Res* 2017;69:384–92.
19 Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med* 1989;8:551–61.
20 Ghaussy NO, Sibbitt WL, Qualls CR. Cigarette smoking, alcohol consumption, and the risk of systemic lupus erythematosus: a case-control study. *J Rheumatol* 2001;28:2449–53.
21 Hardy CJ, Palmer BP, Muir KR, *et al*. Smoking history, alcohol consumption, and systemic lupus erythematosus: a case-control study. *Ann Rheum Dis* 1998;57:451–5.
22 Costenbader KH, Kim DJ, Peerzada J, *et al*. Cigarette smoking and the risk of systemic lupus erythematosus: a meta-analysis. *Arthritis Rheum* 2004;50:849–57.
23 Jiang F, Li S, Jia C. Smoking and the risk of systemic lupus erythematosus: an updated systematic review and cumulative meta-analysis. *Clin Rheumatol* 2015;34:1885–92.
24 Nagata C, Fujita S, Iwata H, *et al*. Systemic lupus erythematosus: a case-control epidemiologic study in Japan. *Int J Dermatol* 1995;34:333–7.
25 Young KA, Terrell DR, Guthridge JM, *et al*. Smoking is not associated with autoantibody production in systemic lupus erythematosus patients, unaffected first-degree relatives, nor healthy controls. *Lupus* 2014;23:360–9.
26 Petruzzelli S, Celi A, Pulerà N, *et al*. Serum antibodies to benzo(a)pyrene diol epoxide-DNA adducts in the general population: effects of air pollution, tobacco smoking, and family history of lung diseases. *Cancer Res* 1998;58:4122–6.
27 Mooney LA, Perera FP, Van Bennekum AM, *et al*. Gender differences in autoantibodies to oxidative DNA base damage in cigarette smokers. *Cancer Epidemiol Biomarkers Prev* 2001;10:641–8.
28 Prummel MF, Wiersinga WM. Smoking and risk of Graves' disease. *JAMA* 1993;269:479–82.
29 Costenbader KH, Feskanich D, Mandl LA, *et al*. Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women. *Am J Med* 2006;119:503.e1–503.e9.
30 Parikh-Patel A, Gold EB, Worman H, *et al*. Risk factors for primary biliary cirrhosis in a cohort of patients from the united states. *Hepatology* 2001;33:16–21.
31 Karlson EW, Lee IM, Cook NR, *et al*. A retrospective cohort study of cigarette smoking and risk of rheumatoid arthritis in female health professionals. *Arthritis Rheum* 1999;42:910–7.
32 Pryor WA, Stone K. Oxidants in cigarette smoke. Radicals, hydrogen peroxide, peroxynitrate, and peroxynitrite. *Ann N Y Acad Sci* 1993;686:12–27.
33 Bauer M, Fink B, Thürmann L, *et al*. Tobacco smoking differently influences cell types of the innate and adaptive immune system-indications from CpG site methylation. *Clin Epigenetics* 2015;7:83.
34 Dogan MV, Shields B, Cutrona C, *et al*. The effect of smoking on DNA methylation of peripheral blood mononuclear cells from African American women. *BMC Genomics* 2014;15:151.
35 Bermudez EA, Rifai N, Buring JE, *et al*. Relation between markers of systemic vascular inflammation and smoking in women. *Am J Cardiol* 2002;89:1117–9.
36 Tracy RP, Psaty BM, Macy E, *et al*. Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. *Arterioscler Thromb Vasc Biol* 1997;17:2167–76.
37 Bijl M, Horst G, Limburg PC, *et al*. Effects of smoking on activation markers, Fas expression and apoptosis of peripheral blood lymphocytes. *Eur J Clin Invest* 2001;31:550–3.
38 Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. *J Autoimmun* 2010;34:J258–J265.
39 Kirkham PA, Spooner G, Rahman I, *et al*. Macrophage phagocytosis of apoptotic neutrophils is compromised by matrix proteins modified by cigarette smoke and lipid peroxidation products. *Biochem Biophys Res Commun* 2004;318:32–7.
40 Kiyohara C, Washio M, Horiuchi T, *et al*. Kyushu Sapporo SLE (KYSS) Study Group. Risk modification by CYP1A1 and GSTM1 polymorphisms in the association of cigarette smoking and systemic lupus erythematosus in a Japanese population. *Scand J Rheumatol* 2012;41:103–9.
41 Arbuckle MR, McClain MT, Rubertone MV, *et al*. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med* 2003;349:1526–33.

EXTENDED REPORT

Anticitrullinated protein/peptide antibody multiplexing defines an extended group of ACPA-positive rheumatoid arthritis patients with distinct genetic and environmental determinants

Johan Rönnelid,[1] Monika Hansson,[2] Linda Mathsson-Alm,[1,3] Martin Cornillet,[4] Evan Reed,[2] Per-Johan Jakobsson,[2] Lars Alfredsson,[5] Rikard Holmdahl,[6] Karl Skriner,[7] Guy Serre,[4] Karin Lundberg,[2] Lars Klareskog[2]

Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-211782).

[1]Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden
[2]Department of Medicine, Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden
[3]Thermo Fisher Scientific, Uppsala, Sweden
[4]Laboratory of Epithelial Differentiation and Rheumatoid Autoimmunity, U1056 Inserm, Toulouse University, Toulouse, France
[5]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[6]Department of Medical Inflammation Research, Karolinska Institutet, Stockholm, Sweden
[7]Department of Medicine, Charité University Hospital, Berlin, Germany

Correspondence to
Dr Johan Rönnelid, Department of Immunology, Genetics and Pathology, Uppsala University, SE-75185 Uppsala, Sweden; johan.ronnelid@igp.uu.se

Received 12 May 2017
Revised 14 September 2017
Accepted 15 September 2017
Published Online First 25 October 2017

To cite: Rönnelid J, Hansson M, Mathsson-Alm L, *et al*. *Ann Rheum Dis* 2018;**77**:203–211.

ABSTRACT

Introduction The second generation anticyclic citrullinated peptide (anti-CCP2) assay detects the majority but not all anticitrullinated protein/peptide antibodies (ACPA). Anti-CCP2-positive rheumatoid arthritis (RA) is associated with HLA-DRB1* shared epitope (SE) alleles and smoking. Using a multiplex assay to detect multiple specific ACPA, we have investigated the fine specificity of individual ACPA responses and the biological impact of additional ACPA reactivity among anti-CCP2-negative patients.

Methods We investigated 2825 patients with RA and 551 healthy controls with full data on anti-CCP2, HLA-DRB1* alleles and smoking history concerning reactivity against 16 citrullinated peptides and arginine control peptides with a multiplex array.

Results The prevalence of the 16 ACPA specificities ranged from 9% to 58%. When reactivity to arginine peptides was subtracted, the mean diagnostic sensitivity increased by 3.2% with maintained 98% specificity. Of the anti-CCP2-negative patients, 16% were found to be ACPA positive. All ACPA specificities associated with SE, and all but one with smoking. Correction for arginine reactivity also conveyed a stronger association with SE for 13/16 peptides. Importantly, when all ACPA specificities were analysed together, SE and smoking associated with RA in synergy among ACPA positive, but not among ACPA-negative subjects also in the anti-CCP2-negative subset.

Conclusions Multiplexing detects an enlarged group of ACPA-positive but anti-CCP2-negative patients with genetic and environmental attributes previously assigned to anti-CCP2-positive patients. The individual correction for arginine peptide reactivity confers both higher diagnostic sensitivity and stronger association to SE than gross ACPA measurement.

INTRODUCTION

The first publication on the highly specific anticitrullinated protein/peptide antibodies (ACPA) already showed that there was vast epitope heterogeneity between individual patients with rheumatoid arthritis (RA).[1] The anticyclic citrullinated peptide 2 (anti-CCP2) assay includes a mixture of peptides aiming at optimising diagnostic sensitivity while keeping the diagnostic specificity high.[2] This test and other general ACPA tests have allowed the subcategorisation of patients with RA with respect to ACPA status.[3 4]

Since the discovery of ACPA, there has been an extensive search for citrullinated autoantigens inside and outside rheumatic joints with an aim to define structures of importance for the initiation and progression of ACPA responses in patients with RA. The list of autoantigens encompasses epitopes on, for example, filaggrin,[5–8] fibrin/fibrinogen,[9–12] vimentin,[13–15] alpha-enolase[16] and collagen type II.[17 18] Such compartmentalisation of the ACPA response has proven useful. In 2009, Madhi *et al* showed that the smoking–HLA-DRB1* shared epitope (SE) association previously attributed to anti-CCP2-positive RA patients was mostly confined to patients double positive for antibodies against CCP2 and CEP-1, the immunodominant citrullinated alpha-enolase epitope, whereas patients single positive for anti-CCP2 showed a much lower degree of association.[16 19] Such studies have since been repeated with larger panels of specific ACPA reactivities including citrullinated vimentin peptides and being used for the immunological subsetting of RA in the context of genes such as SE and PTPN22, as well as smoking.[20 21]

To facilitate such subsetting studies, we have developed a peptide microarray for the parallel detection of autoantibodies against multiple citrullinated peptides. A proof-of-concept study was published in 2012, where we investigated reactivity against 12 different citrullinated peptides in 927 patients with RA and 461 healthy controls from the Epidemiological Investigations in Rheumatoid Arthritis (EIRA) case–control study.[22] We described varying sensitivity at the same predefined high specificity (98%) for individual ACPA, with some of them approaching but never surpassing the anti-CCP2 sensitivity. Although the majority of ACPA peptide-positive patients were also anti-CCP2 positive, there were a considerable number of ACPA peptide-positive patients also in the anti-CCP2 negative subset.

A number of studies have described non-specific anti-CCP2 responses in, for example, tuberculosis,[23 24] hepatitis C,[25 26] autoimmune hepatitis[27] and *Leishmania donovani* infection.[28] Such non-specific responses have been demonstrated by

comparing the ELISA reactivity against the CCP2 with reactivity against identical plates coated with the parallel native peptides containing the original arginine residues instead of citrulline or only blocked wells. Due to conventional assay configuration, such individual controls are almost never performed in routine ACPA testing in clinical laboratories. The microarray format, however, easily allows simultaneous evaluation of reactivity against citrullinated peptides and their arginine-containing counterparts.[22]

In the present study, we have investigated the biological significance of additional ACPA reactivity among anti-CCP2-negative individuals, and we have related each individual ACPA response to reactivity with the analogue arginine-containing peptide.

PATIENTS AND METHODS

Subjects

Patients and controls from the EIRA case-control study were included, for the RA patients within 12 months after first symptoms. Patients were aged between 18 and 70 years and diagnosed according to the 1987 American College of Rheumatology (ACR) criteria by a rheumatologist, and sampling was performed at the first visit before disease-modifying anti-rheumatic drug (DMARD) treatment.[29] Controls were matched for age, sex and residential area. Data on smoking habits were retrieved by questionnaire at inclusion, and patients and controls were genotyped for HLA-DRB1* and grouped in relation to SE alleles. More information about EIRA can be found elsewhere.[3 30]

In total 2934 patients and 624 controls were investigated. Due to the propensities of certain sera (eg, direct binding to all peptides containing streptavidin) and high background reactivity to the microarray surface, 118 samples (74 patients and 44 controls) were excluded. Two patients and two controls lacked anti-CCP2 data, 24 patients and 13 controls lacked information about HLA-DRB1* alleles and smoking information was missing for 24 patients and 13 controls. A total of 109 patients and 73 controls were excluded, leaving 2825 patients and 551 controls for the final analysis.

Serum samples were drawn at the time of inclusion in EIRA and thereafter stored frozen at −70°C. All subjects had given informed consent, and ethical approval was granted by the Karolinska Institutet ethics committee.

ACPA microarray

ACPA reactivity was measured using a custom-made microarray based on the ImmunoCAP ISAC system (Phadia AB, Uppsala, Sweden), originally constructed for evaluation of multiple allergy reactivities.[31 32] A full description of the microarray technology was published previously.[22] Sixteen citrullinated ACPA peptides were investigated (see online supplementary table 1). Reactivity against non-citrullinated arginine-containing control peptides were investigated in parallel for all peptides, except for the citrullinated collagen type II peptide CII359-369 (citC1), where the control peptide is an autoantigen in itself and where the conformational epitopes are destroyed by citrullination.[18] Fluorescense intensities were normalised and expressed as arbitrary units.

Statistics

As ACPA responses are non-normally distributed, non-parametric statistics were used throughout the study. Diagnostic sensitivity was calculated in two ways. In the first (henceforth referred to as gross reactivity), gross data were evaluated and the 98th percentile among the controls were used as cut-off. In the second, net ACPA reactivity defined as the difference in arbitrary units between citrullinated and arginine peptides were calculated, and the 98th percentile for that difference among the controls used as cut-off. Additive sensitivity and specificity was calculated either from the full cohort, or starting from the anti-CCP2 sensitivity of 64.46% (1821/2825 patients positive) and specificity of 98.37% (9/551 controls positive) and thereafter adding the ACPA peptide that added most patients. Thereafter, the process was reiterated seven times, each time defining the ACPA specificity with the highest prevalence in the remaining group, and finally performed for all 16 peptides. For the calculation of the additive sensitivity and specificity for multiple ACPA reactivities as well as for determination of SE and smoking association among anti-CCP2 negative subjects, an alternative 99.5% specificity cut-off was evaluated in parallel. SE and smoking associations were expressed as OR with 95% CIs. Statistics were performed using the JMP11 and Prism 6 softwares.

RESULTS

Use of arginine-subtracted ACPA data conveys higher diagnostic sensitivity and stronger association to SE alleles

To address the question concerning whether correction for background reactivity against arginine peptides would enhance the performance of the assay, the diagnostic sensitivity for individual ACPA peptides was evaluated both using gross and arginine-subtracted data. Out of the 15 peptides investigated in both ways, 12 showed higher diagnostic sensitivity when using arginine-subtracted data. There was a sizeable difference in sensitivity gain by using arginine-subtracted data, with total sensitivity for the two peptides Pept Z2 and Fibα621–635 increasing 10.55% and 7.36%, respectively. The mean increase in diagnostic sensitivity for all ACPA specificities was 3.20% (table 1). For the three peptides where raw data showed the highest sensitivity, the difference was negligible (0.11%–0.25%). Co-occurrence of reactivity against individual citrullinated peptides is described in online supplementary table 2.

We then compared the individual association to SE for 15 peptides using both gross and arginine-subtracted data among the 2825 patients with RA, for each comparison using the negative patients as controls. The arginine-subtracted data yielded higher OR for SE for 12/15 peptides, whereas only 3/15 showed higher OR when gross data were used (table 2). The three peptides showing marginally decreased sensitivity after arginine subtraction (table 1) were also the same showing a marginal decrease in OR. The differences in OR were however small and overlapping between raw and arginine-subtracted data (table 2).

We hypothesised that the increase in sensitivity after subtraction of arginine peptide reactivity might be due to differences between patients and controls concerning reactivity against arginine peptides. Indeed, as shown in (see online supplementary table 3), controls showed higher reactivity to 13/15 arginine-containing peptides than did patients with RA. Thus, individual subtraction of arginine peptide values increased the difference between mostly ACPA-positive patients and mostly ACPA-negative controls.

As arginine-subtracted data both increased the diagnostic sensitivity and association to HLA SE among patients with RA, arginine-subtracted data have been used below.

Table 1 Comparison of diagnostic sensitivity for 16 ACPA peptides between raw data for citrullinated peptides and net data where the responses for the corresponding arginine-containing control peptides had been subtracted from patients and controls before calculation

	Number positive raw data	Diagnostic sensitivity raw data (%)	Number positive arginine-subtracted data	Diagnostic sensitivity arginine-subtracted data (%)	Difference in sensitivity between arginine-subtracted and raw data (%)
Fil307-324 (CCP1)	1193	42.23	1234	43.68	1.45
Vim60-75	1235	43.72	1232	43.61	−0.11
Vim2-17	877	31.04	911	32.25	1.20
Fibβ36–52	1313	46.48	1413	50.02	3.54
Fibα563–583	1134	40.14	1210	42.83	2.69
Fibα580–600	579	20.50	572	20.25	−0.25
Fibα621–635	923	32.67	1131	40.04	7.36
Fibα36–50	458	16.21	467	16.53	0.32
Fibβ60–74	1635	57.88	1631	57.73	−0.14
Eno5-21 (CEP-1)	1332	47.15	1410	49.91	2.76
Pept Z1	1392	49.27	1513	53.56	4.28
Pept Z2	1018	36.04	1316	46.58	10.55
Pept-1	854	30.23	1017	36.00	5.77
Pept-5	1474	52.18	1504	53.24	1.06
Bla-26	859	30.41	900	31.86	1.45
CII359-369 (citC1)	255	9.03	NA	NA	NA
					mean
					3.20
Anti-CCP2 (conventional cut-off)	1821	64.46			

Data are based on investigation of the 2825 RA patients with full anti-CCP2, HLA and smoking data, and the cut-offs were set at the 98% specificity level determined from 551 healthy controls. For comparison, raw data have been included on the collagen peptide where no arginine subtraction has been made. In the bottom right, the mean change in diagnostic sensitivity when using arginine-subtracted data is shown.
ACPA, anticitrullinated protein/peptide antibodies; CCP2, cyclic citrullinated peptide 2; NA, not applicable; RA, rheumatoid arthritis.

Table 2 HLA-DRB1* shared epitope (SE) association for 16 citrullinated peptides among patients with RA from the EIRA cohort

Peptide	No SE Number not reacting/ number reacting Raw data	Any SE Number not reacting/ number reacting Raw data	OR (95% CI) Raw data	No SE Number not reacting/ number reacting Arginine-subtracted data	Any SE Number not reacting/ number reacting Arginine-subtracted data	OR (95% CI) Arginine-subtracted data
Fil307-324 (CCP1)	542/201	1090/992	**2.45 (2.04 to 2.95)**	536/207	1055/1027	***2.52 (2.10 to 3.02)***
Vim60-75	610/133	980/1102	**5.16 (4.20 to 6.34)**	612/131	981/1101	***5.24 (4.26 to 6.45)***
Vim2-17	630/113	1318/764	***3.23 (2.60 to 4.02)***	623/120	1291/791	***3.18 (2.57 to 3.94)***
Fibβ36–52	530/213	982/1100	**2.79 (2.33 to 3.34)**	520/223	892/1190	***3.11 (2.60 to 3.72)***
Fibα563–583	586/157	1105/977	**3.30 (2.71 to 4.01)**	577/166	1038/1044	***3.50 (2.88 to 4.24)***
Fibα580–600	668/75	1578/504	***2.84 (2.20 to 3.69)***	668/75	1585/497	***2.79 (2.16 to 3.62)***
Fibα621–635	607/136	1295/787	**2.71 (2.21 to 3.33)**	567/176	1127/955	***2.73 (2.26 to 3.30)***
Fibα36–50	636/107	1731/351	1.20 (0.95 to 1.52)	634/109	1724/358	*1.21 (0.96 to 1.52)*
Fibβ60–74	510/233	680/1402	***4.51 (3.77 to 5.40)***	511/232	683/1399	***4.51 (3.77 to 5.40)***
Eno5-21 (CEP-1)	573/170	920/1162	**4.26 (3.51 to 5.16)**	559/184	856/1226	***4.35 (3.61 to 5.25)***
Pept Z1	555/188	878/1204	**4.05 (3.36 to 4.88)**	531/212	781/1301	***4.17 (3.48 to 5.01)***
Pept Z2	605/138	1202/880	**3.21 (2.62 to 3.94)**	558/185	951/1131	***3.59 (2.97 to 4.33)***
Pept-1	619/124	1352/730	**2.70 (2.18 to 3.33)**	600/143	1208/874	***3.04 (2.48 to 3.72)***
Pept-5	525/218	826/1256	**3.66 (3.06 to 4.39)**	519/224	802/1280	***3.70 (3.09 to 4.43)***
Bla-26	607/136	1359/723	**2.37 (1.93 to 2.92)**	608/135	1317/765	***2.61 (2.13 to 3.22)***
CII359-369 (citC1)	702/41	1868/214	**1.96 (1.39 to 2.77)**	NA	NA	NA

Data are shown both for raw data and for net data where the responses for the corresponding arginine-containing control peptides had been subtracted for each peptide (arginine-subtracted data). For each ACPA peptide, the OR version showing the strongest association is italicised and significant associations are depicted in bold letters. The reference groups are the patients not reacting with the investigated peptide in that comparison. For comparison, data have been included on the collagen peptide where no arginine subtraction has been made. Data are based on investigation of the 2825 RA patients with full anti-CCP2, HLA and smoking data, and the cut-offs were set at the 98% specificity level determined from 551 healthy controls.
ACPA, anticitrullinated protein/peptide antibodies; CCP2, cyclic citrullinated peptide 2; EIRA, Epidemiological Investigations in Rheumatoid Arthritis; NA, not applicable; RA, rheumatoid arthritis.

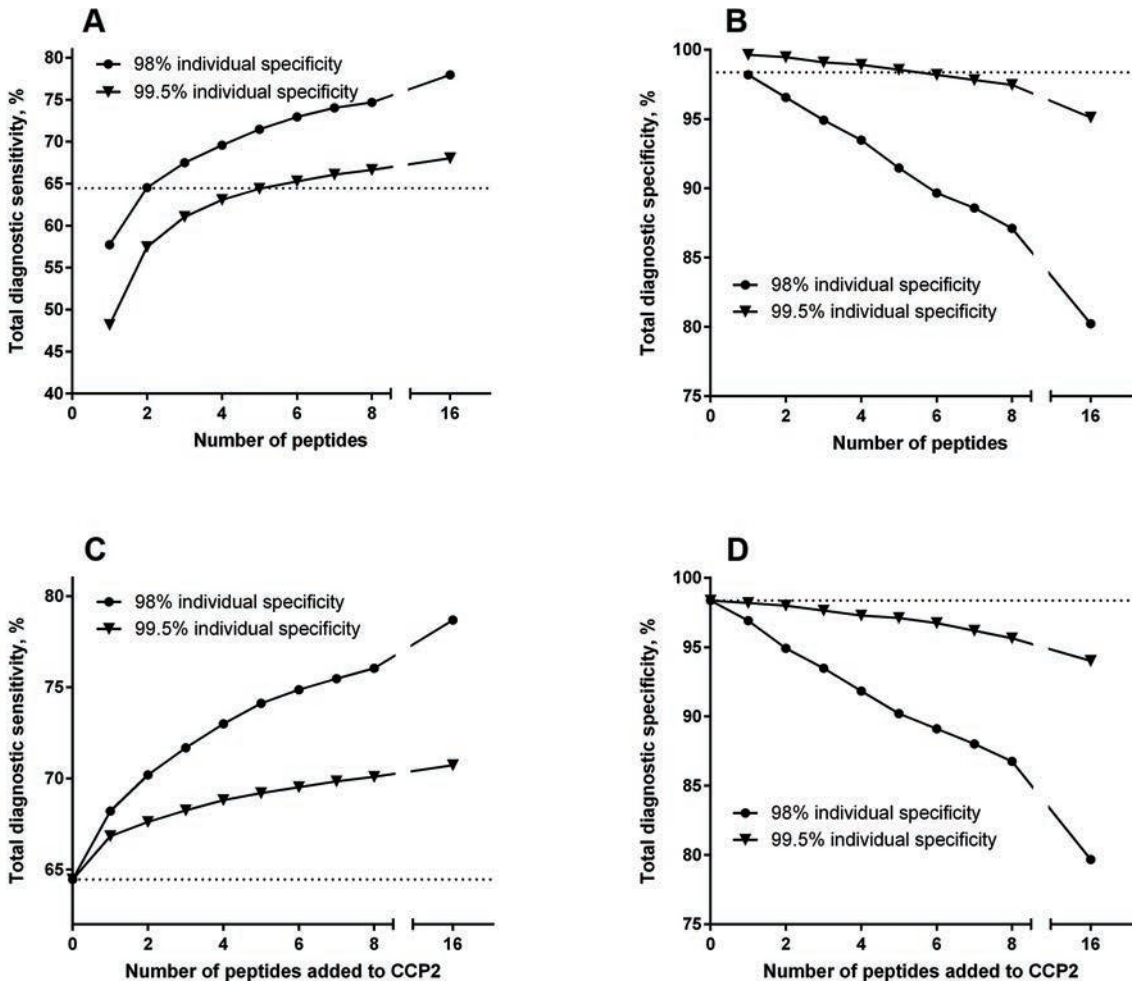


Figure 1 Impact on total (A and C) diagnostic sensitivity and (B and D) diagnostic specificity by sequentially adding the peptide adding most patients. In (A) and (B), all patients were investigated, and in (C) and (D), the anti-CCP2 negative subset. Sensitivity (64.46%) and specificity (98.37%) for anti-CCP2 are marked as horizontal dotted lines. In each panel, two optional lines are shown, based on 98% and 99.5% diagnostic specificity for the individual peptides, determined from 551 healthy controls. In panels (A) and (B), the order of the first eight peptides are Fibβ60-74, Pept-5, Fibβ36-52, Eno5-21, Fibα36-50, Fibα621-635, Pept-1 and Fil307-324 at the 98% specificity level, and Pept-5, Fibβ60-74, Pept-1, Pept-Z1, Fibβ36-52, Eno5-21, Fibβ621-635 and Fil307-324 at the 99.5% specificity level. In panels (C) and (D), the corresponding orders were Fibβ60-74, Fibα36-50, Pept-5, Fibα621-635, Fibβ36-52, Fibα580-600, Pept-1 and Pept-Z1 at the 98% specificity level, and Fibβ60-74, Pept-5, Pept-1, Fibβ36-52, Fibα36-50, Fibα621-635, Eno5-21 and Bla-26 at the 99.5% specificity level. CCP2, cyclic citrullinated peptide 2.

Increase in sensitivity and decrease in specificity by sequentially adding individual peptides to the assay

The individual diagnostic sensitivity for the evaluated peptides are shown in table 1 and varied between 16.53% and 57.73% after arginine subtraction. For the citrullinated type II collagen peptide CII359-369 where no arginine subtraction was performed, the sensitivity was 9.03%.

Thereafter, combinations of individual peptides were evaluated concerning their propensity to identify patients in the full RA group and within the anti-CCP2-negative RA subset. When using 98th percentile cut-offs, sequential addition of peptides increased the sensitivity from 57.73% for 1 peptide to 74.69% for 8 peptides and 77.95% for all 16 peptides. This increase in sensitivity was associated with a drop in diagnostic specificity from 98.19% for one peptide, 87.11% for eight peptides and 80.22% for all 16 peptides. When using 99.5% specificity cut-offs, addition of eight peptides increased the total sensitivity to 66.65% with maintenance of a rather high specificity (97.46%). For all 16 peptides, sensitivity was 68.04% and specificity was 95.10% (figure 1A, B).

Using the 98th percentile cut-off, sequential addition of peptides increased the anti-CCP2 sensitivity (64.46%) to 76.04% for eight added peptides and to 78.69% for all 16 peptides; the corresponding specificities were 98.37% (anti-CCP2 only), 86.75% and 79.67%. With 99.5% percentile cut-offs, addition of eight peptides increased the total sensitivity to 70.09% with 95.64% specificity. For all 16 peptides, sensitivity was 70.73% and specificity was 94.01% (figure 1C, D).

The distribution of number of ACPA specificities is shown in online supplementary figure 1. All patients analysed together showed a bimodal distribution with maxima around 0 and 13 specificities respectively (mean 6.27). This distribution was explained as an overlap of anti-CCP2 positive with mode 13 and mean 9.21 specificities and anti-CCP2-negative patients with mode 0 and mean 0.94 specificities. The low mean for the anti-CCP2-negative patients was however more than three times higher than for the healthy controls with mean 0.30 specificities. Only two controls had more than 4 ACPA specificities, 11 and 14 respectively, and both were anti-CCP2 positive.

Individual peptide reactivity and association to SE and smoking

When RA patients showing reactivity to individual ACPA peptides were compared with patients not reacting with any ACPA peptides, all peptides showed a significant association to SE and all but one associated to a history of ever smoking. The OR for SE association varied between 3.16 and 8.09 (mean OR 5.69, 18.0% coefficiency of variation (CV%)) and was substantially higher than for the association to smoking (OR between 1.34 and 1.98, mean OR 1.71, 8.4 CV%). We thereafter investigated the SE and smoking associations among the anti-CCP2-negative patients for individual peptides. Six out of 16 peptides showed an individual SE association (mean OR for all 16 peptides 1.76, 40.4 CV%), and only 1/16 associated with smoking (mean OR 1.14, 27.7 CV%) and OR was generally much lower and showed higher variability than for the full RA cohort (figure 2 and online supplementary table 4).

The number of ACPA specificities varied with occurrence of SE, with a mean of 3.45 ACPA peptides for SE-negative and 7.28 for SE-positive patients (see online supplementary figure 2). Number of ACPA also related to the number of SE alleles; SE heterozygous patients showed a bimodal distribution very much like the total RA population with a mean of 6.59 peptides, while SE homozygous individuals showed a clear mode around 12, with a mean of 8.67 reactivities. When two-way analysis of variance (ANOVA) was applied using anti-CCP2 and SE status as independent variables, both associated to number of ACPA peptides ($p<0.0001$ for both), with a significant interaction ($p=0.0010$, data not shown).

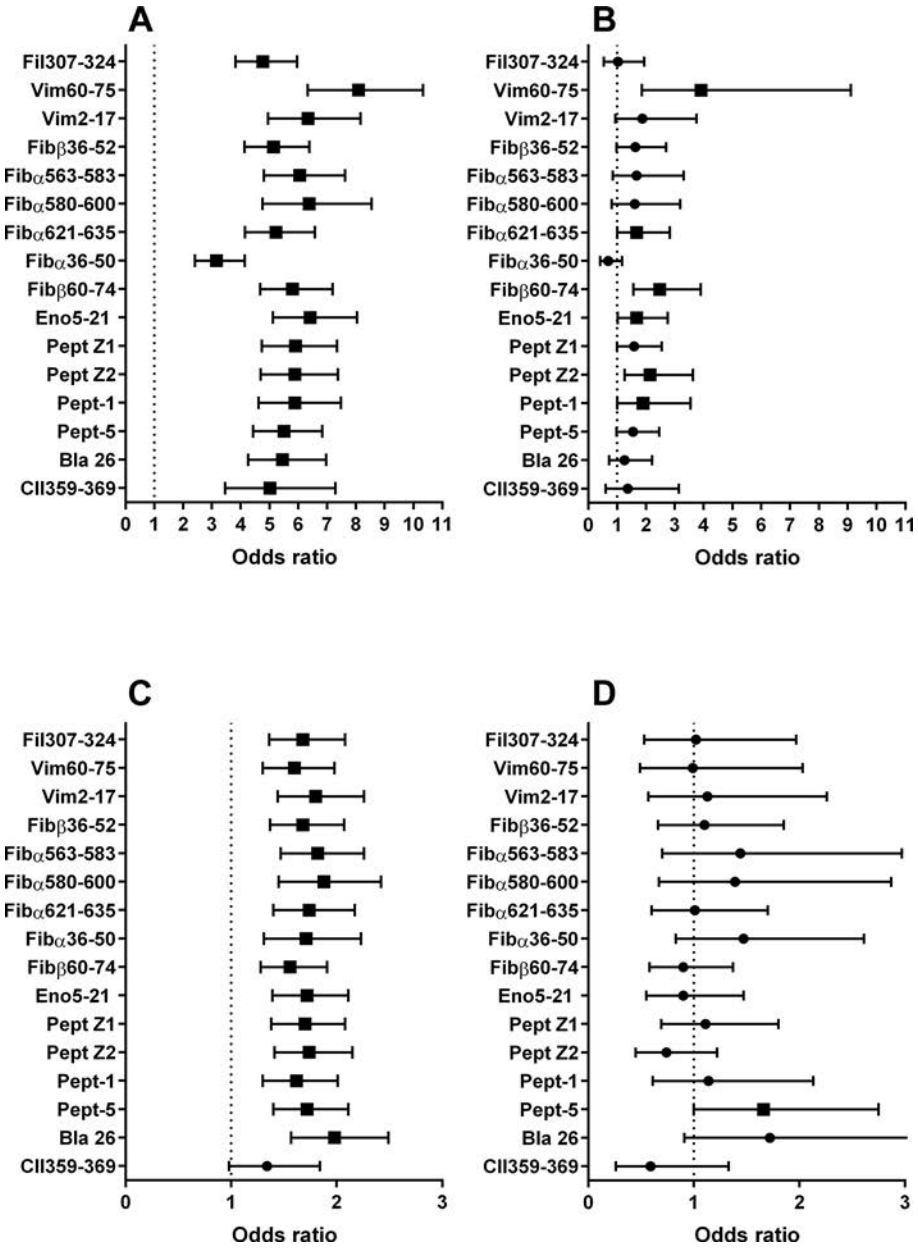


Figure 2 Individual association between (A and B) HLA-DRB1* shared epitope or (C and D) smoking with the occurrence of antibodies against 16 citrullinated peptides among 2825 RA patients. Analysis was performed for both (A and C) all patients and (B and D) the anti-CCP2-negative patient subset (n=1004). Arginine control values have been subtracted before calculation for the first 15 peptides, and raw data have been used for the collagen type II peptide CII359-369. Cut-off was set at the 98th percentile for 551 healthy controls. Results are shown as ORs with 95% CIs. ORs for significant associations are depicted as filled quadrants and for non-significant associations as filled circles. The corresponding figures are shown in online supplementary table 4. CCP2, cyclic citrullinated peptide 2.

A history of smoking also associated with higher number of ACPA specificities: never smokers reacted with a mean of 5.14 peptides, whereas ever smokers had 6.79 peptide reactivities as a mean (see online supplementary figure 2). Although this smoking association partly depended on the co-occurrence with HLA SE, a significant difference (p=0.0035) remained between the number of ACPA specificities among SE negative never smokers (mean 2.59, median 1) and SE negative ever smokers (mean 3.90, median 1; data not shown). Two-way ANOVA confirmed that number of ACPA specificities associated with both ever smoking status and SE (p<0.0001 for both), but without any interaction (p=0.55, data not shown).

Among anti-CCP2-negative patients HLA SE and smoking act in synergy as risk factors for ACPA peptide-positive but not for ACPA peptide-negative RA

We next investigated whether ACPA peptide reactivity associate with RA risk independent of anti-CCP2. Anti-CCP2-negative subjects (1004 patients with RA and 542 controls) were investigated in relation to SE and smoking history. As the combination of any of 16 peptide reactivities at the 98% specificity level creates a very low specificity (figure 1), we defined ≥2 peptide reactivities as the cut-off for general ACPA peptide positivity, in agreement with a previous publication.[33] Occurrence of SE together with smoking history associated with significantly increased OR for RA (OR 3.55, CI 1.24 to 10.14), but only among ACPA-positive subjects (figure 3A, B and table 3). Also, using the 99.5% cut-off for individual peptides, SE and smoking history in synergy associated with RA risk among ACPA peptide positive (OR 3.86, CI 1.08 to 13.83) but not among ACPA-negative subjects in the anti-CCP2-negative subgroup (figure 3C, D and online supplementary table 5).

When using a 98% specificity cut-off for individual peptides and regarding ≥1 reactivity as positive, the corresponding association remained barely significant (OR 1.86; CI 1.02 to 3.39; see online supplementary table 6).

DISCUSSION

In this study we have shown that our ACPA microarray defines an ACPA-positive subgroup among anti-CCP2-negative patients that shows the same HLA SE/smoking association as previously described for anti-CCP2-positive patients. Indeed, our figure 3 on anti-CCP2-negative subjects dichotomised according to ACPA reactivity mimics a previously published figure on unselected patients with RA from EIRA dichotomised according to anti-CCP2 status although with smaller statistical effect.[3]

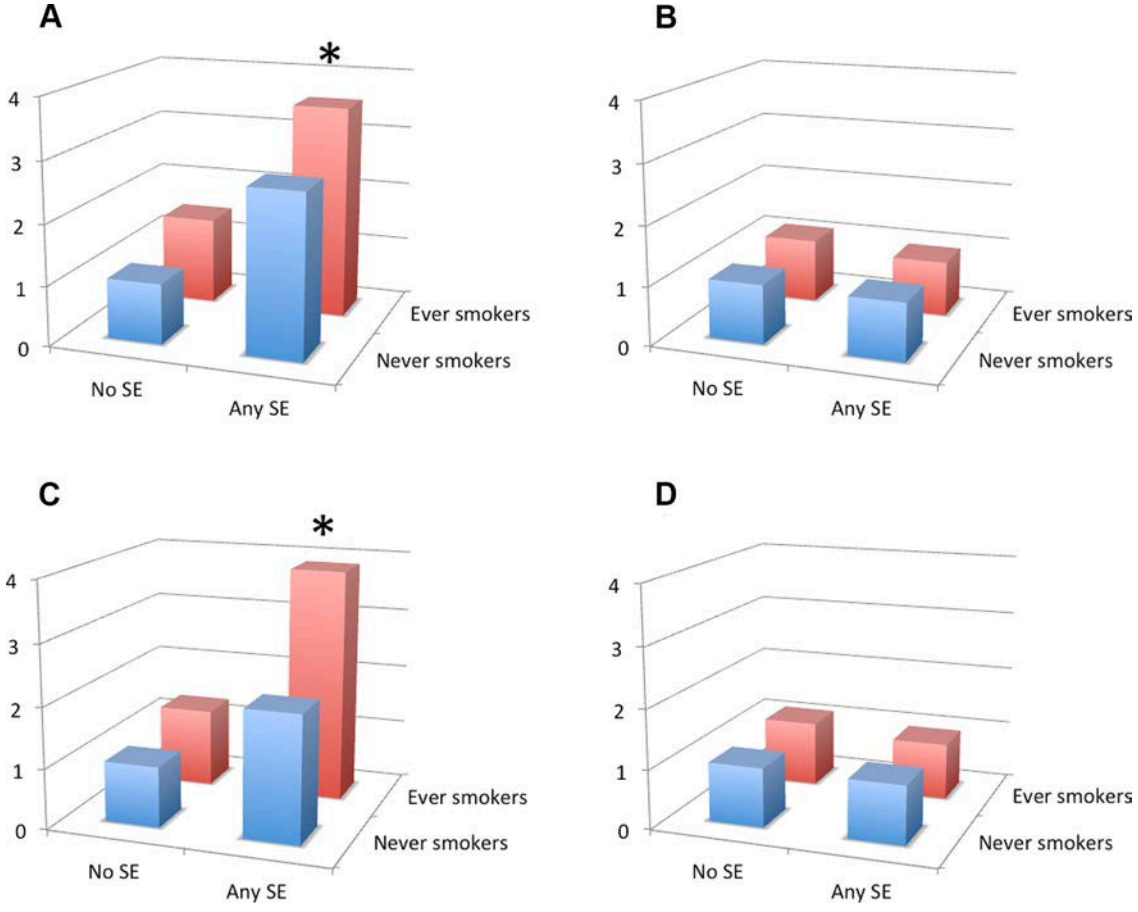


Figure 3 ORs for developing RA among anti-CCP2 negative subjects in relation to HLA-DRB1* SE alleles and a history of smoking, including 1004 RA patients and 542 healthy controls. In (A) and (B), ACPA positivity was defined as reacting with ≥2 peptides where the cut-off for each individual peptide was set at the 98th percentile of 551 healthy controls, and in (C) and (D) ACPA was defined as reacting with ≥1 peptide at the 99.5% specificity level. In (A) and (C) data are shown for ACPA peptide positive patients and in (B) and (D) data for ACPA peptide negative individuals are depicted. Significant OR with CI not involving one are shown with an asterisk. Full statistical data are shown in table 3 for panels (A) and (B), and online supplementary table 5 for panels (C) and (D). ACPA, anticitrullinated protein/peptide antibodies; CCP2, cyclic citrullinated peptide 2; RA, rheumatoid arthritis; SE, shared epitope.

Table 3 Association to RA diagnosis for reactivity against 16 citrullinated peptides, HLA SE and smoking among anti-CCP2-negative subjects

	No SE Controls	No SE Cases	OR (95% CI)	Any SE positive controls	Any SE positive cases	OR (95% CI)	Single SE positive controls	Single SE positive cases	OR (95% CI)	Double SE positive controls	Double SE positive cases	OR (95% CI)
Peptide positive	19	68	(ref)	13	121	*2.60 (1.21 to 5.59)*	12	93	2.16 (0.98 to 4.76)	1	28	7.82 (1.00 to 61.29)
Peptide positive Never smokers	9	26	(ref)	5	39	2.70 (0.81 to 8.97)	5	25	1.73 (0.51 to 5.88)	0	14	10.40 (0.56 to 191.9)*
Peptide positive Ever smokers	10	42	1.45 (0.52 to 4.05)	8	82	*3.55 (1.24 to 10.14)*	7	68	*3.36 (1.14 to 9.96)*	1	14	4.85 (0.56 to 42.26)
Peptide negative	238	401	(ref)	272	414	0.90 (0.72 to 1.13)	221	352	0.94 (0.75 to 1.19)	51	62	0.72 (0.48 to 1.08)
Peptide negative Never smokers	94	150	(ref)	102	160	0.98 (0.69 to 1.41)	87	135	0.97 (0.67 to 1.41)	15	25	1.04 (0.52 to 2.08)
Peptide negative Ever smokers	144	251	1.09 (0.79 to 1.52)	170	254	0.94 (0.68 to 1.29)	134	217	1.02 (0.72 to 1.42)	36	37	0.64 (0.38 to 1.09)

Data are based on 1546 anti-CCP2 negative individuals (1004 RA patients and 542 controls) with complete data on anti-CCP2, HLA-SE and smoking. Out of them, 242 (208 patients and 34 controls) are positive for ≥2 of the 16 peptides (peptide positive), and 1304 (796 RA patients and 508 controls) are positive for 0–1 peptides (peptide negative). Arginine-subtracted data were used for the 15 non-collagen ACPA peptides and raw data for the collagen peptide. Cut-offs for the 16 individual peptides were set at the 98% specificity level determined from 551 healthy controls. Significant associations are italicised. The corresponding data are graphically depicted in figure 3A,B.
ACPA, anticitrullinated protein/peptide antibodies; CCP2, cyclic citrullinated peptide 2; RA, rheumatoid arthritis; SE, shared epitope. *OR was calculated by adding 0.5 to each value.

Therefore, it is plausible that the use of additional peptides can diagnose an extended group of ACPA-positive patients that will respond to therapies like anti-CCP2-positive patients.

Individual sample correction for reactivity against arginine peptides both increases diagnostic sensitivity and slightly increases association to SE among the patients. As shown in online supplementary table 3, arginine peptide reactivities were higher among controls than among patients with RA for most peptides, thus explaining a larger difference between mostly ACPA-negative controls and mostly ACPA-positive patients after individual subtraction of arginine peptide reactivity. In our previous proof of concept study, we raised the question on whether subtraction of reactivity against arginine peptides would enhance assay performance.[22] Including more peptides and patients, we, this time, obtained quite unequivocal results showing that arginine subtraction yields a considerable increase in diagnostic sensitivity at an unchanged specificity level, together with increased association to SE among patients with RA for the majority of peptides. The microarray format easily allows such sample specific controls to be performed. Among routine clinical diagnostic tests, very few ACPA assays include such sample-specific normalisation, as that would imply almost the double number of ELISA wells needed and thus a considerable increase in cost per patient analysis.

Sample-specific normalisation is however not generally used in other ACPA multiplexing formats, for example, in the recently published study by Wagner *et al*[33] using addressable laser bead immunoassay.

In a recent study by van Heemst *et al*[34] using the same assay but considerably fewer samples, no association was found between SE and smoking among anti-CCP2 negative subjects. In that study, the mean +2 SDs among controls were used as cut-off for each peptide in an additive manner, thus creating a considerably lower total specificity. When using a comparable low-specificity approach, also our corresponding results became considerably weaker, although our study includes >5 times more patients with SE data than the Leiden study. We conclude that to be meaningful, microarrayed ACPA tests have to be combined with high specificity approaches.

In our study, 118 samples were excluded due to specific properties of the individual sera, including general sticky binding to the microarray surface and general background reactivity to all streptavidin-containing spots. In the absence of individual controls and control over the full reaction surface, such sera would probably be regarded as positive for the measured analyte. We found only two controls with a high number of ACPA reactivities, and both belonged to the minority (9/551) of anti-CCP2-positive controls. Hypothetically, these two individuals might be in a pre-RA phase, as the number of ACPA peptide reactivities increase during the years before RA diagnosis.[35] We believe that our assay format helped us to exclude non-assessable samples, with ensuing clear difference in frequency distribution between anti-CCP2-positive and anti-CCP2-negative patients as shown in online supplementary figure 1B and C.

Using the eight most discriminatory peptides and high individual specificity (99.5%), the total sensitivity was increased by 5.5% as compared with anti-CCP2 alone, with the preservation of total specificity of 95.64%. This implies that 16% of the anti-CCP2-negative patients can be diagnosed as ACPA positive with a total specificity in agreement recommendations for rheumatoid factor in the previous ACR classification criteria (>95%), which is the only directive so far for cut-off setting for RA autoantibodies.[29]

This assay has been used to study the sequential appearance of individual ACPA reactivities the years predating RA.[35] We envisage that this assay can be used to study which ACPA reactivities might appear in patients with arthralgia and in first-degree relatives of patients with RA as has previously been done with isotypes of anti-CCP2 and rheumatoid factor.[36]

In conclusion, our study demonstrates that the multiplex assay can identify a substantial proportion of anti-CCP2-negative patients that display ACPA reactivities, and in addition that this subset of patients with RA shows similarities with the classical anti-CCP2-positive RA group concerning major genetic and environmental determinants. This extended group of ACPA-positive patients will most likely use similar molecular pathways towards disease and respond similar to therapies as anti-CCP2-positive patients where therapeutic responses are contingent on ACPA status.

Acknowledgements The authors would want to thank the EIRA study group for including patients. This study was supported by grants from the Swedish Research Council, the Swedish Rheumatism Association, King Gustav V 80-year Foundation and the Be The Cure EU consortium.

Contributors JR had full access to all data, is responsible for data integrity, made statistical calculations and drafted the manuscript. JR, MH, LM-A and LK conceived the study. LA provided epidemiological data and statistical expertise. MH and LM-A participated in the development of the ISAC microarray and performed the laboratory work on the EIRA cohort. MC, ER, P-JJ, RH, KS, GS and KL provided peptides for the analyses, including validation of their performance. All authors read, commented on and approved the final manuscript.

Competing interests The project is part of the Innovative Medicines Initiative (IMI) project Be The Cure where Karolinska Institutet is a scientific partner and Thermo Fisher Scientific is a commercial partner. The project follows the rules for IMI projects. JR has obtained reagents from Thermo Fisher Scientific for the investigation on other rheumatology cohorts. LM-A is employed by Thermo Fisher Scientific. LK and RH were cofounders of a company, Curara AB, which has previously collaborated with Thermo Fisher Scientific concerning certain technical aspects of the multiplex assay. This development is done with partial support from an ERC Proof of Concept Grant (pRActice) to LK. RH is a coinventor of a patent (US Patent 7148020) protecting the use of the CitC1 and C1 peptides. KS is coinventor of the patents US 13/141,960 and EP 09799354.7 describing the diagnostic use of the hnRNP-A3 peptide epitopes. GS is coinventor of several international patents about ACPA antigens held by BioMérieux Cy and licenced to Eurodiagnostica Cy and Axis-Shield Cy for commercialisation of the CCP2 assays; according to French laws, he receives a part of the royalties paid to the Toulouse III University and the University Hospital of Toulouse. KL is coinventor of patent US12/524,465, describing the diagnostic use of the CEP-1 epitope. The other authors declare that they have no competing interests.

Ethics approval The ethics board in Stockholm.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All relevant data are available in the manuscript and supplementary files.

REFERENCES

1 Schellekens GA, de Jong BA, van den Hoogen FH, *et al*. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. *J Clin Invest* 1998;101:273–81.
2 van Venrooij WJ, van Beers JJ, Pruijn GJ. Anti-CCP antibodies: the past, the present and the future. *Nat Rev Rheumatol* 2011;7:391–8.
3 Klareskog L, Stolt P, Lundberg K, *et al*. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum* 2006;54:38–46.
4 Pedersen M, Jacobsen S, Garred P, *et al*. Strong combined gene-environment effects in anti-cyclic citrullinated peptide-positive rheumatoid arthritis: a nationwide case-control study in Denmark. *Arthritis Rheum* 2007;56:1446–53.
5 Simon M, Girbal E, Sebbag M, *et al*. The cytokeratin filament-aggregating protein filaggrin is the target of the so-called "antikeratin antibodies," autoantibodies specific for rheumatoid arthritis. *J Clin Invest* 1993;92:1387–93.
6 Sebbag M, Simon M, Vincent C, *et al*. The antiperinuclear factor and the so-called antikeratin antibodies are the same rheumatoid arthritis-specific autoantibodies. *J Clin Invest* 1995;95:2672–9.
7 Girbal-Neuhauser E, Durieux JJ, Arnaud M, *et al*. The epitopes targeted by the rheumatoid arthritis-associated antifilaggrin autoantibodies are posttranslationally generated on various sites of (pro)filaggrin by deimination of arginine residues. *J Immunol* 1999;162:585–94.
8 Schellekens GA, Visser H, de Jong BA, *et al*. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. *Arthritis Rheum* 2000;43:155–63.
9 Masson-Bessière C, Sebbag M, Girbal-Neuhauser E, *et al*. The major synovial targets of the rheumatoid arthritis-specific antifilaggrin autoantibodies are deiminated forms of the alpha- and beta-chains of fibrin. *J Immunol* 2001;166:4177–84.
10 Sebbag M, Moinard N, Auger I, *et al*. Epitopes of human fibrin recognized by the rheumatoid arthritis-specific autoantibodies to citrullinated proteins. *Eur J Immunol* 2006;36:2250–63.
11 Iobagiu C, Magyar A, Nogueira L, *et al*. The antigen specificity of the rheumatoid arthritis-associated ACPA directed to citrullinated fibrin is very closely restricted. *J Autoimmun* 2011;37:263–72.
12 Hermansson M, Artemenko K, Ossipova E, *et al*. MS analysis of rheumatoid arthritic synovial tissue identifies specific citrullination sites on fibrinogen. *Proteomics Clin Appl* 2010;4:511–8.
13 Snir O, Widhe M, Hermansson M, *et al*. Antibodies to several citrullinated antigens are enriched in the joints of rheumatoid arthritis patients. *Arthritis Rheum* 2010;62:44–52.
14 Verpoort KN, Cheung K, Ioan-Facsinay A, *et al*. Fine specificity of the anti-citrullinated protein antibody response is influenced by the shared epitope alleles. *Arthritis Rheum* 2007;56:3949–52.
15 Vossenaar ER, Després N, Lapointe E, *et al*. Rheumatoid arthritis specific anti-Sa antibodies target citrullinated vimentin. *Arthritis Res Ther* 2004;6:R142–50.
16 Kinloch A, Tatzer V, Wait R, *et al*. Identification of citrullinated alpha-enolase as a candidate autoantigen in rheumatoid arthritis. *Arthritis Res Ther* 2005;7:R1421–9.
17 Burkhardt H, Koller T, Engström A, *et al*. Epitope-specific recognition of type II collagen by rheumatoid arthritis antibodies is shared with recognition by antibodies that are arthritogenic in collagen-induced arthritis in the mouse. *Arthritis Rheum* 2002;46:2339–48.
18 Uysal H, Bockermann R, Nandakumar KS, *et al*. Structure and pathogenicity of antibodies specific for citrullinated collagen type II in experimental arthritis. *J Exp Med* 2009;206:449–62.
19 Mahdi H, Fisher BA, Källberg H, *et al*. Specific interaction between genotype, smoking and autoimmunity to citrullinated alpha-enolase in the etiology of rheumatoid arthritis. *Nat Genet* 2009;41:1319–24.
20 Lundberg K, Bengtsson C, Kharlamova N, *et al*. Genetic and environmental determinants for disease risk in subsets of rheumatoid arthritis defined by the anticitrullinated protein/peptide antibody fine specificity profile. *Ann Rheum Dis* 2013;72:652–8.
21 van der Woude D, Alemayehu WG, Verduijn W, *et al*. Gene-environment interaction influences the reactivity of autoantibodies to citrullinated antigens in rheumatoid arthritis. *Nat Genet* 2010;42:814–6.
22 Hansson M, Mathsson L, Schlederer T, *et al*. Validation of a multiplex chip-based assay for the detection of autoantibodies against citrullinated peptides. *Arthritis Res Ther* 2012;14:R201.
23 Elkayam O, Segal R, Bendayan D, *et al*. The anti-cyclic citrullinated peptide response in tuberculosis patients is not citrulline-dependent and sensitive to treatment. *Arthritis Res Ther* 2010;12:R12.
24 Kakumanu P, Yamagata H, Sobel ES, *et al*. Patients with pulmonary tuberculosis are frequently positive for anti-cyclic citrullinated peptide antibodies, but their sera also react with unmodified arginine-containing peptide. *Arthritis Rheum* 2008;58:1576–81.
25 Bassyouni IH, Ezzat Y, Hamdy S, *et al*. Clinical significance of anti-cyclic citrullinated peptide antibodies in Egyptian patients with chronic hepatitis C virus genotype IV infection. *Clin Chem Lab Med* 2009;47:842–7.
26 Orge E, Cefle A, Yazici A, *et al*. The positivity of rheumatoid factor and anti-cyclic citrullinated peptide antibody in nonarthritic patients with chronic hepatitis C infection. *Rheumatol Int* 2010;30:485–8.
27 Vannini A, Cheung K, Fusconi M, *et al*. Anti-cyclic citrullinated peptide positivity in non-rheumatoid arthritis disease samples: citrulline-dependent or not? *Ann Rheum Dis* 2007;66:511–6.
28 Åhlin E, Elshafie AI, Nur MA, *et al*. Anti-citrullinated peptide antibodies in sudanese patients with Leishmania donovani infection exhibit reactivity not dependent on citrullination. *Scand J Immunol* 2015;81:201–8.
29 Arnett FC, Edworthy SM, Bloch DA, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
30 Stolt P, Bengtsson C, Nordmark B, *et al*. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. *Ann Rheum Dis* 2003;62:835–41.
31 Deinhofer K, Sevcik H, Balic N, *et al*. Microarrayed allergens for IgE profiling. *Methods* 2004;32:249–54.
32 Hiller R, Laffer S, Harwanegg C, *et al*. Microarrayed allergen molecules: diagnostic gatekeepers for allergy treatment. *Faseb J* 2002;16:414–6.

33 Wagner CA, Sokolove J, Lahey LJ, *et al*. Identification of anticitrullinated protein antibody reactivities in a subset of anti-CCP-negative rheumatoid arthritis: association with cigarette smoking and HLA-DRB1 'shared epitope' alleles. *Ann Rheum Dis* 2015;74:579–86.
34 van Heemst J, Trouw LA, Nogueira L, *et al*. An investigation of the added value of an ACPA multiplex assay in an early rheumatoid arthritis setting. *Arthritis Res Ther* 2015;17:276.
35 Brink M, Hansson M, Mathsson L, *et al*. Multiplex analyses of antibodies against citrullinated peptides in individuals prior to development of rheumatoid arthritis. *Arthritis Rheum* 2013;65:899–910.
36 Ärlestig L, Mullazehi M, Kokkonen H, *et al*. Antibodies against cyclic citrullinated peptides of IgG, IgA and IgM isotype and rheumatoid factor of IgM and IgA isotype are increased in unaffected members of multicase rheumatoid arthritis families from northern Sweden. *Ann Rheum Dis* 2012;71:825–9.

OPEN ACCESS

EXTENDED REPORT

Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate)

Dinesh Khanna,[1] Christopher P Denton,[2] Celia J F Lin,[3] Jacob M van Laar,[4] Tracy M Frech,[5] Marina E Anderson,[6] Murray Baron,[7] Lorinda Chung,[8] Gerhard Fierlbeck,[9] Santhanam Lakshminarayanan,[10] Yannick Allanore,[11] Janet E Pope,[12] Gabriela Riemekasten,[13] Virginia Steen,[14] Ulf Müller-Ladner,[15] Helen Spotswood,[16] Laura Burke,[16] Jeffrey Siegel,[3] Angelika Jahreis,[3] Daniel E Furst[17]

Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-211682).

For numbered affiliations see end of article.

Correspondence to
Dr Dinesh Khanna, Division of Rheumatology, Department of Internal Medicine, University of Michigan Scleroderma Program, Ann Arbor MI 48109, USA; khannad@med.umich.edu

Received 21 April 2017
Revised 15 September 2017
Accepted 19 September 2017
Published Online First
26 October 2017

ABSTRACT

Objectives Assess the efficacy and safety of tocilizumab in patients with systemic sclerosis (SSc) in a phase II study.

Methods Patients with SSc were treated for 48 weeks in an open-label extension phase of the faSScinate study with weekly 162 mg subcutaneous tocilizumab. Exploratory end points included modified Rodnan Skin Score (mRSS) and per cent predicted forced vital capacity (%pFVC) through week 96.

Results Overall, 24/44 (55%) placebo-tocilizumab and 27/43 (63%) continuous-tocilizumab patients completed week 96. Observed mean (SD (95% CI)) change from baseline in mRSS was –3.1 (6.3 (–5.4 to –0.9)) for placebo and –5.6 (9.1 (–8.9 to–2.4)) for tocilizumab at week 48 and –9.4 (5.6 (–8.9 to –2.4)) for placebo-tocilizumab and –9.1 (8.7 (–12.5 to –5.6)) for continuous-tocilizumab at week 96. Of patients who completed week 96, any decline in %pFVC was observed for 10/24 (42% (95% CI 22% to 63%)) placebo-tocilizumab and 12/26 (46% (95% CI 27% to 67%)) continuous-tocilizumab patients in the open-label period; no patients had >10% absolute decline in %pFVC. Serious infection rates/100 patient-years (95% CI) were 10.9 (3.0 to 27.9) with placebo and 34.8 (18.0 to 60.8) with tocilizumab during the double-blind period by week 48 and 19.6 (7.2 to 42.7) with placebo-tocilizumab and 0.0 (0.0 to 12.2) with continuous-tocilizumab during the open-label period.

Conclusions Skin score improvement and FVC stabilisation in the double-blind period were observed in placebo-treated patients who transitioned to tocilizumab and were maintained in the open-label period. Safety data indicated increased serious infections in patients with SSc but no new safety signals with tocilizumab.

Trial registration number NCT01532869; Results.

INTRODUCTION

Systemic sclerosis (SSc) is a rare, debilitating autoimmune disorder of the connective tissue and vasculature that is characterised by inflammation, fibrosis and microvascular injury of multiple organs.[1–3] Patients with SSc experience high morbidity and mortality rates,[2] particularly those who have pulmonary, cardiac or renal organ involvement.[4] Indeed, lung disease is the primary cause of scleroderma-related deaths.[1 5] Few treatment options are available for patients with SSc, and there is an unmet need for disease-modifying therapy.[6]

Interleukin 6 (IL-6) appears to play a role in SSc pathogenesis.[7 8] Patients with SSc have increased IL-6 expression in endothelial cells and skin fibroblasts.[9] Serum IL-6 levels are elevated in patients with SSc,[10 11] particularly those with early diffuse cutaneous skin involvement.[12 13] Furthermore, some studies have suggested a role for IL-6 as a marker for disease progression and clinical outcome in patients with SSc.[11] C reactive protein (CRP) is correlated with IL-6, and CRP levels are elevated in patients with active SSc, especially those with early diffuse cutaneous SSc.[14]

Tocilizumab is a monoclonal anti–IL-6 receptor-α antibody for the treatment of patients with rheumatoid arthritis, systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis and giant cell arteritis.[15] Initial investigations of tocilizumab in patients with SSc demonstrated improvements in skin sclerosis and SSc-associated polyarthritis.[16 17] The faSScinate clinical trial was the first double-blind, randomised controlled trial investigating the efficacy and safety of subcutaneous tocilizumab in patients with SSc. Results from the 48-week double-blind period of faSScinate, including the primary end point, were published previously and demonstrated that treatment with tocilizumab resulted in a clinically meaningful but not statistically significant decline in modified Rodnan Skin Score (mRSS) compared with placebo through week 48 for patients receiving tocilizumab.[18] Exploratory efficacy results and safety through week 96 of the faSScinate trial, including the 48-week open-label period, are now reported.

METHODS

Study design

faSScinate was a multicentre, randomised, double-blind, placebo-controlled, two-arm, parallel-group, phase II clinical trial conducted at 35 hospitals across Canada, France, Germany, the UK and USA. The study design and patient enrolment criteria have been published.[18] Briefly, the 96-week trial consisted of a 48-week double-blind period

To cite: Khanna D, Denton CP, Lin CJF, *et al*. *Ann Rheum Dis* 2018;**77**:212–220.

followed by a 48-week open-label period. Patients were randomly assigned (1:1) to receive weekly subcutaneous injections of tocilizumab 162 mg or placebo during the 48-week double-blind period (tocilizumab group or placebo group, respectively) with the option for escape therapy with methotrexate, hydroxychloroquine or mycophenolate mofetil (MMF) after 24 weeks if they had worsening SSc. Randomisation was stratified according to joint involvement at baseline (<4 or ≥4 joints on the 28 tender joint count). At week 48, all patients in the tocilizumab and placebo groups transitioned to open-label weekly injections of tocilizumab 162 mg for another 48 weeks (continuous-tocilizumab and placebo-tocilizumab groups, respectively).

Patients

Eligible patients were 18 years of age or older; received a diagnosis of SSc according to the 1980 American College of Rheumatology Criteria,[19] with less than 5 years since their first non-Raynaud's sign or symptom; had an mRSS score of 15 to 40 with clinical skin involvement proximal to the elbows, knees or both, with or without facial involvement; and had active disease. Active disease was defined as at least one of the following features at screening: increase ≥3 in mRSS units compared with the last visit within the previous 1 month to 6 months or new-onset SSc within 1 year before screening, involvement of one new body area with ≥2 mRSS units or two new body areas with ≥1 mRSS unit, documentation of worsening skin thickening (patients with new-onset SSc only), or ≥1 tendon friction rub plus CRP level ≥10 mg/L, erythrocyte sedimentation rate ≥28 mm/hour or platelet count ≥330 × 10^3/μL. All patients provided written informed consent.

Assessments

Exploratory efficacy end points included mean change from baseline to week 96 in mRSS; proportions of patients with improvements in mRSS of ≥20%, ≥40% and ≥60%; proportions of patients achieving minimal clinically important difference (MCID) in mRSS (change from baseline of ≥4.7)[20]; per cent predicted forced vital capacity (%pFVC); per cent predicted diffusing capacity for carbon monoxide corrected for haemoglobin (%pDLCO (Hb corr)) and Clinician Global Visual Analogue Scale (VAS). Patient-reported outcomes included Health Assessment Questionnaire–Disability Index (HAQ-DI), Patient Global VAS, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Score and Pruritus 5-D Itch Scale. Safety was reported as rates of adverse events (AEs) and serious AEs (SAEs) per 100 patient-years (PY) with 95% CIs.

Statistical analysis

Although a mixed-model, repeated-measures analysis was performed on the placebo-controlled period at weeks 24 and 48, observed data were analysed for the week 96 period because all end points during the open-label period were exploratory. Exploratory efficacy end points in the open-label period were assessed in the modified intent-to-treat population (all randomly assigned patients who received any study drug). Safety was

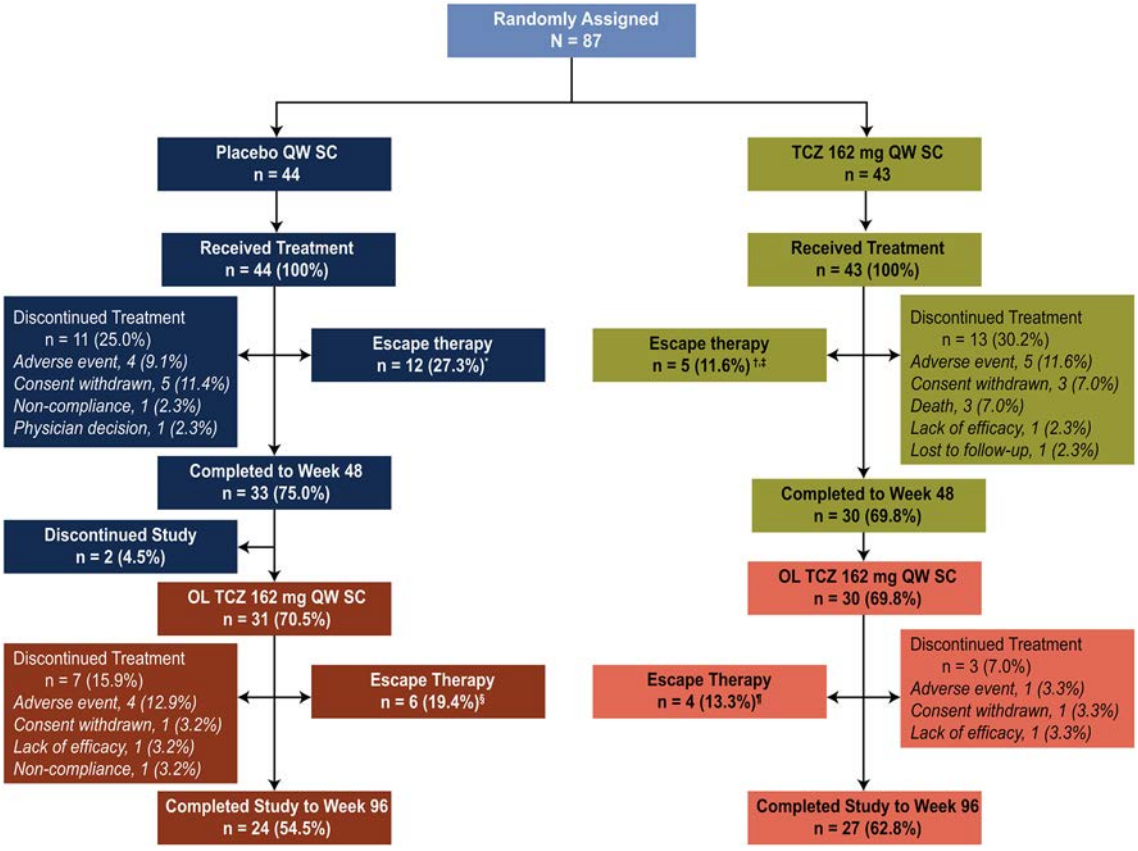


Figure 1 Patient disposition (intent-to-treat population). *Methotrexate, n=5; hydroxychloroquine, n=2; mycophenolate mofetil, n=5. †Methotrexate, n=2; hydroxychloroquine, n=2; mycophenolate mofetil, n=1. ‡One patient who continued as an escape patient at week 48[18] was later removed by the site and was not included at week 96. §Methotrexate, n=1; hydroxychloroquine, n=1; mycophenolate mofetil, n=4 (1 patient who received mycophenolate mofetil in the double-blind period and received it again in the open-label period was not counted in the open-label period). ¶Hydroxychloroquine, n=2; mycophenolate mofetil, n=2. OL, open-label; QW, every week; SC, subcutaneously; TCZ, tocilizumab.

Table 1 Baseline demographics and disease characteristics (safety population)

	Patients randomly assigned in the double-blind period		Patients who transitioned to the open-label period*	
	Placebo QW SC n=44	Tocilizumab 162 mg QW SC n=43	Placebo- tocilizumab 162 mg QW SC n=31	Continuous-tocilizumab 162 mg QW SC n=30
Age, years	48 (12.9)	51 (11.7)	47 (11.9)	52 (11.8)
Female, n (%)	35 (80)	32 (74)	26 (84)	23 (77)
White, n (%)	40 (91)	38 (88)	28 (90)	26 (87)
Duration of SSc, months	19.5 (17.0)	17.6 (13.9)§	20.0 (18.2)	17.7 (13.5)
Total mRSS†	25.6 (5.9)	26.4 (7.2)	24.6 (5.4)	25.2 (6.9)
TJC28	7.4 (8.5)‡	7.4 (8.9)	8.3 (9.1)	8.1 (10.0)
TJC28 ≥4, n (%)	21 (49)‡	20 (47)	16 (52)	12 (40)
Overall HAQ-DI Score	1.4 (0.7)	1.3 (0.6)§	1.2 (0.7)	1.2 (0.6)¶
Clinician Global VAS, mm	60.9 (15.2)	64.1 (15.1)	57.9 (15.2)	62.5 (15.7)
Patient Global VAS, mm	61.9 (21.0)	59.8 (18.3)	60.2 (22.9)	56.6 (18.3)
FACIT-Fatigue	26.5 (11.6)‡	25.6 (11.4)	27.9 (12.1)**	26.2 (10.5)
Pruritus 5-D Itch	13.5 (5.1)‡	13.1 (4.5)§	13.2 (4.8)**	13.0 (4.2)¶
CRP, mg/L	10.3 (13.5)‡	10.0 (13.5)	7.7 (7.2)	7.4 (12.7)
%pFVC	82 (13)§	80 (14)	83 (14)**	78 (13)
%pDLCO (Hb corr)	74 (21)‡	73 (19)§	75 (23)**	73 (17)

All values are mean (SD) unless stated otherwise.
*Original baseline data for patients who entered the OL period.
†Possible scores: mRSS, 0–51; HAQ-DI, 0–3; Clinician Global VAS, 0–100; ULN for CRP, 3 mg/L.
‡n = 43.
§n = 42.
¶n = 29.
**n = 30.
%pDLCO (Hb corr), per cent predicted diffusing capacity of the lung for carbon monoxide corrected for haemoglobin; %pFVC, per cent predicted forced vital capacity; CRP, C reactive protein; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire–Disability Index; mRSS, modified Rodnan Skin Score; QW, every week; SC, subcutaneously; SSc, systemic sclerosis; TJC28, tender joint count based on 28 joints; ULN, upper limit of normal; VAS, Visual Analogue Scale.

assessed in all patients who received study drug and provided at least one safety assessment after treatment (safety population) and was summarised by treatment received. The study was not designed or powered for formal statistical comparison of the two treatment arms within the open-label period or with the original tocilizumab arm at week 48 because of inherent biases of open-label results. However, 95% CIs were calculated as descriptive statistics using the Pearson Clopper method for exact binomial, and CIs for rates of AEs were based on Poisson distribution.[21] Data from escape patients were not censored.

RESULTS

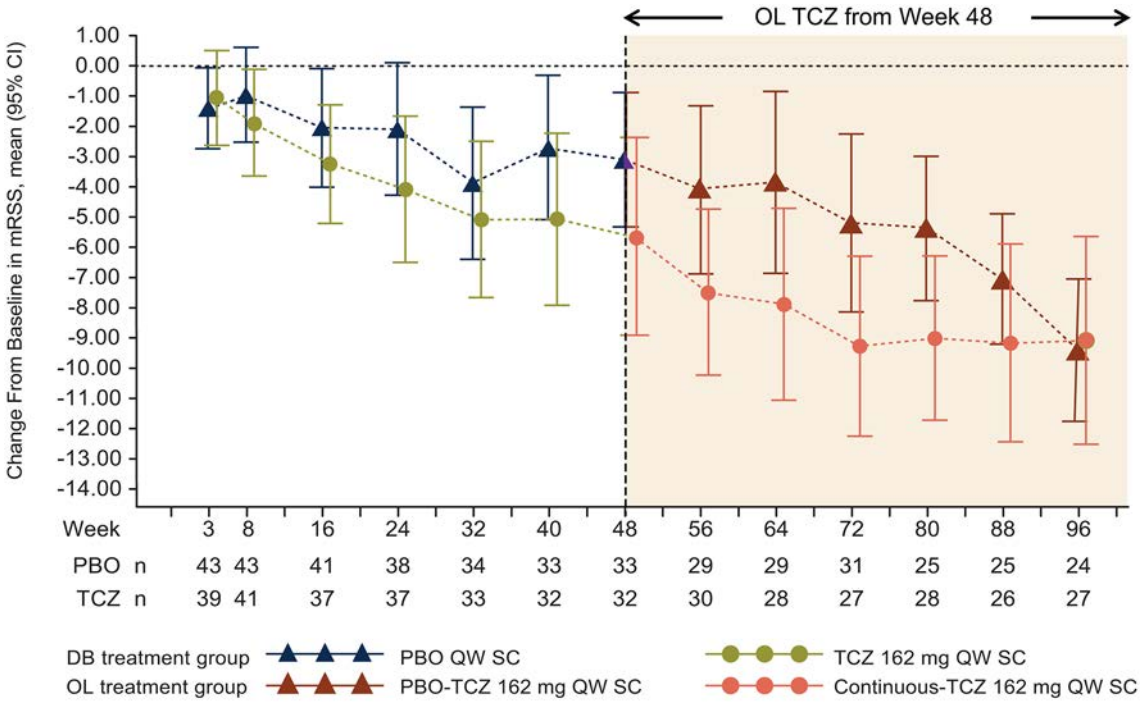
Patients

Eighty-seven patients were enrolled in the faSScinate trial (figure 1); in the double-blind period, 44 patients were originally assigned to receive weekly subcutaneous placebo (placebo group) and 43 patients were originally assigned to receive weekly subcutaneous tocilizumab 162 mg (tocilizumab group). At week 48, 31 (70.5%) patients originally assigned to double-blind placebo transitioned to open-label weekly tocilizumab 162 mg (placebo-tocilizumab group) and 30 (69.8%) patients originally assigned to double-blind tocilizumab transitioned to open-label weekly subcutaneous tocilizumab 162 mg (continuous-tocilizumab group) until they completed the study or withdrew from treatment. Twenty-four (54.5%) patients in the placebo-tocilizumab group and 27 (62.8%) patients in the continuous-tocilizumab group completed week 96. During the open-label period, five patients discontinued because of AEs (four patients in the placebo-tocilizumab group and one patient in the continuous-tocilizumab group). Other reasons for study withdrawal were non-compliance (one patient in the placebo-tocilizumab group), lack of efficacy (one patient in each treatment group) and patient consent withdrawn (one patient in each treatment group). Escape therapy was received by 18 patients originally assigned to receive placebo (12 in the placebo group during the double-blind period and 6 in the placebo-tocilizumab group during the open-label period) and by 9 patients originally assigned to receive tocilizumab (5 in the tocilizumab group during the double-blind period and 4 in the continuous-tocilizumab group during the open-label period) (figure 1).

Baseline characteristics were similar between patients who were randomly assigned in the double-blind period and those who transitioned to open-label treatment, with the exception of HAQ-DI scores and CRP values, which were numerically lower, on average, in patients who transitioned to the open-label period (table 1).

Efficacy

Improvements in mRSS were observed during the double-blind period with tocilizumab treatment (mean (SD; 95% CI) change from baseline to week 48: –5.6 (9.1; –8.9 to –2.4)). In addition to the –5.6 improvement from baseline to week 48 with tocilizumab treatment, further improvement was seen in the open-label period, bringing the total mean improvement to –9.1 (8.7; –12.5 to –5.6) from baseline to week 96 (figure 2). Furthermore, patients in the placebo group experienced similar improvements after receiving open-label tocilizumab from week 48 to week 96 (figure 2) (mean (SD; 95% CI) change from baseline –3.1 (6.3; –5.4 to –0.9) to week 48 during double-blind placebo treatment and –9.4 (5.6; –11.8 to –7.0) to week 96 after 48 weeks of open-label tocilizumab treatment). There were incremental improvements between weeks 48 and 96 in the proportions of patients who experienced improvements in mRSS of ≥20%, ≥40% and



	PBO		TCZ	
Wk	Mean (SD) [95% CI] change from BL	Mean (SD) [95% CI] observed score	Mean (SD) [95% CI] change from BL	Mean (SD) [95% CI] observed score
24	-2.1 (6.7) [-4.3, 0.1]	23.2 (9.3) [20.2, 26.3]	-4.1 (7.3) [-6.5, -1.7]	21.8 (9.9) [18.5, 25.1]
48	-3.1 (6.3) [-5.4, -0.9]	22.3 (8.1) [19.4, 25.1]	-5.6 (9.1) [-8.9, -2.4]	19.6 (10.1) [15.9, 23.2]
72	-5.2 (7.9) [-8.1, -2.3]	19.8 (8.0) [16.9, 22.7]	-9.3 (7.5) [-12.2, -6.3]	16.0 (9.1) [12.4, 19.7]
96	-9.4 (5.6) [-11.8, -7.0]	15.3 (7.6) [12.1, 18.6]	-9.1 (8.7) [-12.5, -5.6]	16.2 (9.8) [12.3, 20.1]

Figure 2 Mean change (95% CI) in mRSS from baseline to week 96 (intent-to-treat population; observed data). Negative values denote improvement. Patients randomly assigned to PBO 162 mg QW SC received OL TCZ 162 mg QW SC from week 48. BL, baseline; DB, double-blind; mRSS, modified Rodnan Skin Score; OL, open-label; PBO, placebo; %pFVC, per cent predicted forced vital capacity; QW, every week; SC, subcutaneously; TCZ, tocilizumab.

≥60% and change in mRSS equal to or greater than the MCID of 4.7 units in the continuous-tocilizumab group (table 2).

Improvements in Clinician Global VAS and patient-reported outcomes, as indicated by negative change in HAQ-DI, Clinician Global VAS, and Patient Global VAS and positive change in FACIT-Fatigue Score, observed at week 48 in the tocilizumab group were maintained through the open-label period in the continuous-tocilizumab group (table 2). Furthermore, greater improvements in patient-reported outcomes were observed in placebo-tocilizumab patients after they switched to tocilizumab during the open-label period than during the double-blind placebo period. Patients in the placebo group experienced mean (95% CI) changes from baseline in HAQ-DI of 0.17 (0.05 to 0.30) after 48 weeks of double-blind placebo treatment and –0.29 (–0.46 to –0.13) at week 96 after 48 weeks of open-label tocilizumab treatment (placebo-tocilizumab). Changes from baseline in Clinician Global VAS were –7.69 (–15.06 to –0.32) and –20.61 (–29.52 to –11.7), respectively, changes in Patient Global VAS were –4.03 (–12.42 to 4.36) and –23.75 (–38.95 to –3.46), respectively, and changes in FACIT-Fatigue Scores were 1.37 (–1.37 to 4.11) and 11.26 (5.72 to 16.81), respectively.

Among patients who completed the study to week 96 (completers analysis), similar proportions in both treatment groups experienced worsening in %pFVC (figure 3); 42% of patients in the placebo-to-cilizumab group and 46% of patients in the continuous-tocilizumab group had absolute decreases (>0) in %pFVC during the open-label period from weeks 48 to 96 compared with 83% of patients receiving placebo and 54% of patients receiving tocilizumab during the double-blind period from weeks 0 to 48. During the open-label period, no patients in either treatment group who completed week 96 or withdrew experienced >10% absolute decline in %pFVC after receiving tocilizumab, in contrast to three in the placebo group and one in the tocilizumab group during the double-blind period.

Safety

SAE rates (95% CIs) were 76.1 (50.6–110.0) in the placebo group and 66.7 (42.3–100.1) in the tocilizumab group by week

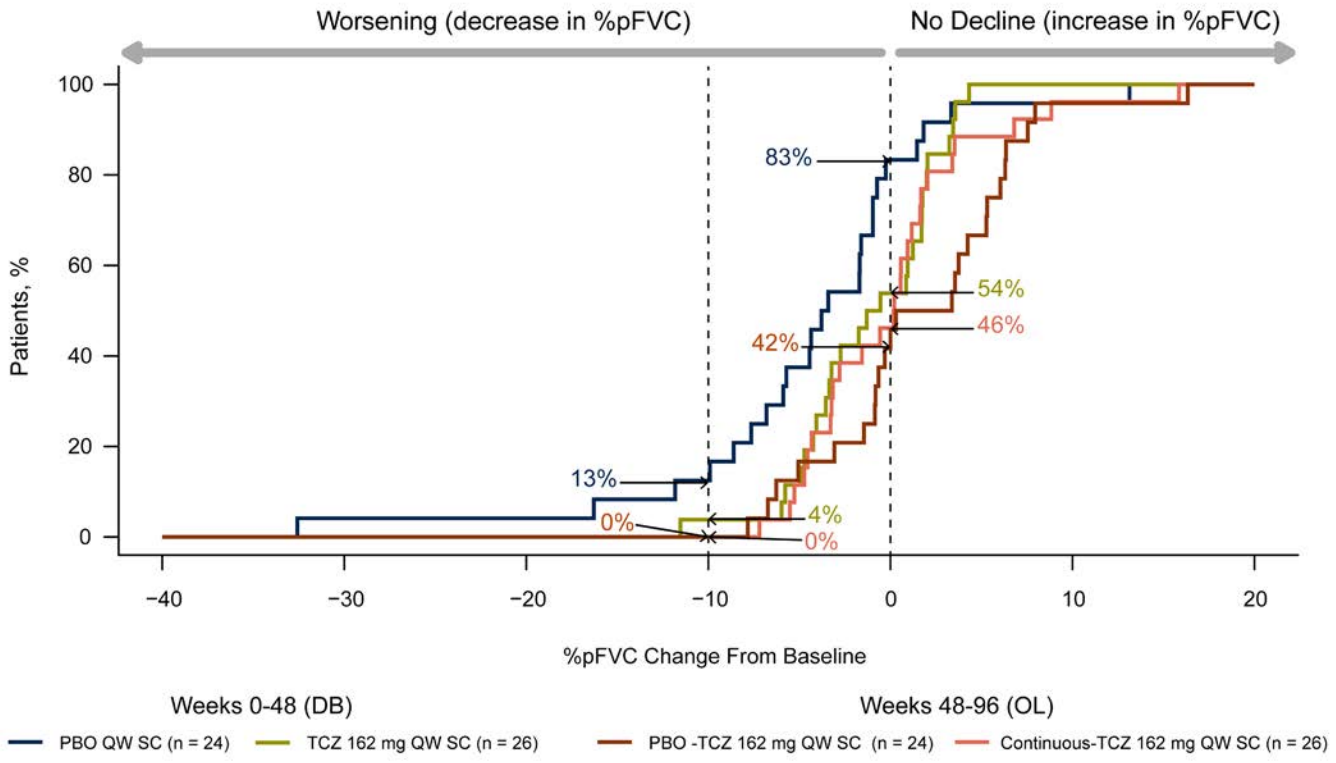
Table 2 Change from baseline to week 48 (double-blind period) or week 96 (including open-label period) in exploratory end points (intent-to-treat population; observed data)

	Double-blind period, week 48		Open-label period, week 96	
	Placebo QW SC n=44	Tocilizumab 162 mg QW SC n=43	Placebo- tocilizumab 162 mg QW SC n=31	Continuous-tocilizumab 162 mg QW SC n=30
Change from baseline in mRSS, n (% (95% CI))*				
≥ 20%	13 (29.5 [16.8 to 45.2])	18 (41.9 [27.0 to 57.9])	18 (40.9 [26.3 to 56.8])	22 (51.2 [35.5 to 66.7])
≥ 40%	3 (6.8 [1.4 to 18.7])	10 (23.3 [11.8 to 38.6])	13 (29.5 [16.8 to 45.2])	15 (34.9 [21.0 to 50.9])
≥ 60%	0 (0.0 [0.0 to 8.0])	5 (11.6 [3.9 to 25.1])	7 (15.9 [6.6 to 30.1])	6 (14.0 [5.3 to 27.9])
≥4.7 units (MCID)[20]	12 (27.3 [15.0, 42.8]) n=33	18 (41.9 [27.0, 57.9]) n=32	19 (43.2 [28.3, 59.0]) n=24	22 (51.2 [35.5, 66.7]) n=27
TJC28, mean (95% CI) change from baseline	−0.97 (−2.85 to 0.91)	−2.28 (−4.16 to −0.40)	−4.88 (−7.99 to −1.76)	−3.39 (−6.14 to −0.65)
[min, max]	[−16, 12] n=33	[−14, 9] n=32	[−23, 2] n=24	[−25, 7] n=28
HAQ-DI, mean (95% CI) change from baseline†	0.17 (0.05 to 0.30)	−0.01 (−0.25 to 0.23)	−0.29 (−0.46 to −0.13)	−0.13 (−0.33 to 0.08)
[min, max]	[−0.63, 0.88] n=34	[−1.13, 1.75] n=31	[−1.25, 0.50] n=24	[−1.25, 1.38] n=27
Clinician Global VAS, mean (95% CI) change from baseline†	−7.69 (−15.06 to −0.32)	−18.57 (−26.89 to −10.25)	−20.61 (−29.52 to −11.7)	−21.30 (−31.05 to −11.54)
[min, max]	[−45, 39] n=32	[−60, 14] n=30	[−57, 21] n=23	[−73, 14] n=27
Patient Global VAS, mean (95% CI) change from baseline†	−4.03 (−12.42 to 4.36)	−9.13 (−18.68 to 0.43)	−23.75 (−38.95 to −8.55)	−11.11 (−18.75 to −3.46)
[min, max]	[−64, 57] n=34	[−59, 36] n=32	[−90, 38] n=24	[−44, 33] n=28
FACIT-Fatigue score, mean (95% CI) change from baseline†	1.37 (−1.37 to 4.11)	3.69 (0.34 to 7.04)	11.26 (5.72 to 16.81)	4.15 (1.51 to 6.79)
[min, max]	[−18.0, 15.0] n=32	[−15.0, 22.0] n=32	[−15.0, 29.0] n=23	[−10.0, 19.0] n=27
Pruritus 5-D Itch Score, mean (95% CI) change from baseline†	−1.87 (−3.26 to −0.48)	−2.03 (−3.91 to −0.16)	−4.43 (−6.32 to −2.55)	−3.23 (−5.38 to −1.09)
[min, max]	[−10, 5] n=30	[−15, 7] n=30	[−14, 1] n=23	[−14, 9} n=26
%pFVC, mean (95% CI) change from baseline	−0.06 (−0.10 to −0.03)	−0.02 (−0.04 to 0.00)	−0.03 (−0.07 to 0.01)	−0.01 (−0.03 to 0.02)
[min, max]	[−0.33, 0.13] n=32	[−0.15, 0.04] n=30	[−0.25, 0.20] n=25	[−0.15, 0.15] n=28
% pDLCO (Hb corr), mean (95% CI) change from baseline	−0.03 (−0.07 to 0.01)	−0.03 (−0.06 to 0.00)	−0.03 (−0.10 to 0.05)	−0.03 (−0.08 to 0.01)
[min, max]	[−0.23, 0.28] n=31	[−0.26, 0.12] n=27	[−0.71, 0.25] n=24	[−0.25, 0.21] n=25

n denotes number of patients with valid assessments at the time point. Escape data were not censored.
*Percentages were calculated based on n=43 (tocilizumab) and n=44 (placebo), the intent-to-treat population; thus, patients with missing change in mRSS Scores were considered non-responders.
†Negative change from baseline indicated improvement for all efficacy measures except FACIT-Fatigue, FVC and DLCO, for which positive change from baseline indicated improvement.
%pDLCO (Hb corr), per cent predicted diffusing capacity of lung for carbon monoxide corrected for haemoglobin; %pFVC, per cent predicted forced vital capacity; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire–Disability Index; max, maximum; MCID, minimal clinically important difference; min, minimum; mRSS, modified Rodnan Skin Score; QW, every week; SC, subcutaneously; TJC28, tender joint count based on 28 joints; VAS, Visual Analogue Scale.

48 compared with 36.0 (18.0–64.4) in the placebo-tocilizumab group and 16.5 (5.4–38.5) in the continuous-tocilizumab group from week 48 to week 96 (table 3). Infections were the most frequently reported AEs and SAEs during double-blind tocilizumab treatment and in placebo patients who transitioned to open-label tocilizumab. In the placebo-tocilizumab group, rates of serious infection increased after the switch to open-label tocilizumab; the rate (95% CI) of serious infections was 10.9 (3.0–27.9) per 100 PY during the 48 weeks of double-blind placebo treatment compared with 19.6 (7.2–42.7) per 100 PY from week 48 to 96, with four patients (12.9%) in this group reporting at least one serious infection after switching to open-label tocilizumab (see online supplementary appendix table 1 for details of serious infections). Patients in the tocilizumab group had a serious infection rate of 34.8 (95% CI 18.0 to 60.8) per 100 PY by week 48. No serious infections were reported after the switch from double-blind to open-label tocilizumab (continuous-tocilizumab).

No deaths were reported during the open-label period in either treatment group, and no serious hepatic AEs, anaphylactic reactions, gastrointestinal perforations or demyelination SAEs were reported during the 96-week treatment period. Changes in laboratory parameters of interest for tocilizumab, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, neutrophil counts and platelet counts, were usually ≤5× the upper limit of normal (ULN) over the 96-week treatment period.



	Weeks 0-48 (DB)		Weeks 48-96 (OL)	
	PBO QW SC (n = 24)	TCZ 162 mg QW SC (n = 26)	PBO-TCZ 162 mg QW SC (n = 24)	Continuous-TCZ 162 mg QW SC (n = 26)
%pFVC change from baseline, n (%) [95% CI]				
Absolute decrease >0	20 (83) [63, 95]	14 (54) [33, 73]	10 (42) [22, 63]	12 (46) [27, 67]
Absolute decrease >10%	3 (13) [3, 32]	1 (4) [0, 20]	0 (0) [0, 14]	0 (0) [0, 13]

Figure 3 Cumulative distribution plot of change from baseline in %pFVC (completers analysis). Data for TCZ 162 mg QW SC and PBO 162 mg QW SC treatment groups show change from baseline to week 48. Patients receiving PBO-TCZ 162 mg QW SC and continuous-TCZ 162 mg QW SC started OL TCZ from week 48 (mean (SD) %pFVC at week 48 was 0.78 (0.14) for the PBO group and 0.80 (0.11) for the TCZ group), and change from week 48 to week 96 is shown. Only patients with data at week 96 are included in any arm (completers); one completer had a missing FVC assessment at week 96 and was excluded from the completers analysis. DB, double-blind; OL, open-label; PBO, placebo; %pFVC, per cent predicted forced vital capacity; QW, every week; SC subcutaneously; TCZ, tocilizumab.

ALT elevation >5× ULN was reported in one patient receiving placebo and one patient receiving tocilizumab during the double-blind period and one placebo-tocilizumab patient after switching to open-label tocilizumab. AST elevation >5× ULN was reported in one patient receiving placebo during the double-blind period (see online supplementary appendix table 2).

DISCUSSION

The phase II faSScinate Study was the first double-blind, randomised controlled trial to show evidence of a potential disease-modifying effect in patients with SSc. By week 48, at the end of the double-blind period of the study, treatment with tocilizumab was associated with clinically relevant, though not statistically significant, improvements in skin thickness measured by mRSS and lung function measured by %pFVC.[18] It has been suggested that tocilizumab may be the first efficient, molecularly targeted treatment for patients with SSc.[22]

Results from the open-label period of the faSScinate trial show that patients originally assigned to receive placebo in the double-blind period who transitioned to open-label tocilizumab at week 48 experienced improvements in mRSS by week 96 that were similar to those of patients who received tocilizumab throughout the study. Furthermore, patients originally assigned to receive tocilizumab during the double-blind period maintained and continued the improvements in mRSS observed during the first 48 weeks of treatment on receiving another 48 weeks of open-label tocilizumab. Although the mean change in mRSS appeared to flatten from week 72 in the continuous-tocilizumab group,

Table 3 Adverse events (AEs, safety population)

	Double-blind period		Open-label period	
	Placebo QW SC n=44	Tocilizumab 162 mg QW SC n=43	Placebo-tocilizumab 162 mg QW SC n=31	Continuous-tocilizumab 162 mg QW SC n=30
Exposure, PY	36.8	34.5	30.6	30.3
AEs, n	244	283	126	153
Rate/100 PY (95% CI)	663.5 (582.9 to 752.2)	820.6 (727.8 to 922.0)	412.4 (343.5 to 491.0)	504.4 (427.6 to 590.9)
SAEs, n	28	23	11	5
Rate/100 PY (95% CI)	76.1 (50.6 to 110.0)	66.7 (42.3 to 100.1)	36.0 (18.0 to 64.4)	16.5 (5.4 to 38.5)
Patients with ≥1 SAE, n (%)	16 (36.4)	14 (32.6)	7 (22.6)	4 (13.3)
Patients with ≥1 serious infection, n (%)*	3 (6.8)	9 (20.9)	4 (12.9)	0
AEs leading to death, n	1	3	0	0
Rate/100 PY	2.72	8.70	0.00	0.00
Patients with AEs leading to withdrawal, n (%)	5 (11.4)	6 (14.0)	4 (12.9)†	0
Rate/100 PY	13.60	17.40	13.09	0.00
Patients with injection site reactions, n*	2 (4.5)	3 (7.0)	4 (12.9)	1 (3.3)
SAEs according to system organ class,‡ number of events (rate/100 PY [95% CI])				
Infections and infestations	4 (10.9 [3.0 to 27.9])	12 (34.8 [18.0 to 60.8])	6 (19.6 [7.2 to 42.7])	0 (0.0 [0.0 to 12.2])
Cardiac disorders	5 (23.6 [4.4 to 31.7])	1 (2.9 [0.1 to 16.2])	0 (0.0 [0.0 to 12.1])	1 (3.3 [0.1 to to 18.4])
Gastrointestinal disorders	6 (16.3 [6.0 to 35.5])	1 (2.9 [0.1 to 16.2])	0 (0.0 [0.0 to 12.1])	0 (0.0 [0.0 to 12.2])
Musculoskeletal and connective tissue disorders	2 (5.4 [0.7 to 19.7])	2 (5.8 [0.7 to 21.0])	1 (3.3 [0.1 to 18.2])	0 (0.0 [0.0 to 12.2])
Skin and subcutaneous tissue disorders	2 (5.4 [0.7 to 19.7])	2 (5.8 [0.7 to 21.0])	0 (0.0 [0.0 to 12.1])	1 (3.3 [0.1 to 18.4])
Vascular disorders	4 (10.9 [3.0 to 27.9])	1 (2.9 [0.1 to 16.2])	0 (0.0 [0.0 to 12.1])	0 (0.0 [0.0 to 12.2])
Blood and lymphatic system disorders	1 (2.7 [0.1 to 15.2])	1 (2.9 [0.1 to 16.2])	1 (3.3 [0.1 to 18.2])	0 (0.0 [0.0 to 12.2])
Renal and urinary disorders	2 (5.4 [0.7 to 19.7])	0 (0.0 [0.0 to 10.7])	1 (3.3 [0.1 to 18.2])	0 (0.0 [0.0 to 12.2])
General disorders and administration site conditions	0 (0.0 [0.0 to 10.0])	2 (5.8 [0.7 to 21.0])	0 (0.0 [0.0 to 12.1])	0 (0.0 [0.0 to 12.2])
Neoplasms, benign, malignant and unspecified	0 (0.0 [0.0 to 10.0])	0 (0.0 [0.0 to 10.7])	1 (3.3 [0.1 to 18.2])	1 (3.3 [0.1 to 18.4])
Nervous system disorders	2 (5.4 [0.7 to 19.7])	0 (0.0 [0.0 to 10.7])	0 (0.0 [0.0 to 12.1])	0 (0.0 [0.0 to 12.2])
Endocrine disorders	0 (0.0 [0.0 to 10.0])	0 (0.0 [0.0 to 10.7])	0 (0.0 [0.0 to 12.1])	1 (3.3 [0.1 to 18.4])
Psychiatric disorders	0 (0.0 [0.0 to 10.0])	1 (2.9 [0.1 to 16.2])	0 (0.0 [0.0 to 12.1])	0 (0.0 [0.0 to 12.2])
Reproductive system and breast disorders	0 (0.0 [0.0 to 10.0])	0 (0.0 [0.0 to 10.7])	0 (0.0 [0.0 to 12.1])	1 (3.3 [0.1 to 18.4])
Respiratory, thoracic and mediastinal disorders	0 (0.0 [0.0 to 10.0])	0 (0.0 [0.0 to 10.7])	1 (3.3 [0.1 to 18.2])	0 (0.0 [0.0 to 12.2])

*Multiple occurrences in the same patient are counted once.
†Osteomyelitis (one case serious, one case not serious), scleroderma renal crisis and breast cancer metastatic.
‡According to the Medical Dictionary for Regulatory Activities, version 18.0.
AEs, adverse events; PY, patient-years; QW, every week; SAEs, serious adverse events; SC, subcutaneously.

there were improvements for individual patients between weeks 72 and 96. Of the 27 patients receiving continuous tocilizumab who completed the study through week 96, 14/27 (52%) had further, primarily modest, improvements (range, −1 to −8 change in mRSS). However, there were two outliers who experienced considerable worsening (+9 and +14 change in mRSS) during this period. Overall, this culminates in a flattened average response. The potential for improvement may be more limited at this time point; 7/27 (26%) patients among the continuous tocilizumab completers had observed mRSS scores ≤9 at week 72 compared with 2/24 (8%) among the placebo-tocilizumab group.

Improvements from weeks 48 to 96 in mRSS were supported by improvements in patient-reported outcomes, including HAQ-DI, Patient Global VAS and FACIT-Fatigue Scores, observed in patients initially assigned to placebo who transitioned to open-label tocilizumab and were comparable to those of patients who received tocilizumab continuously, consistent with trends observed with tocilizumab treatment during the double-blind period.[18] Consistent as well with exploratory analyses in the double-blind period showing fewer tocilizumab-treated (10%) than placebo-treated (23%) patients experienced absolute decline (>10%) in %pFVC after 48 weeks,[18] no patients who completed week 96 of the study experienced >10% decline in %pFVC during the open-label period while receiving tocilizumab. Of note, the primary end point was change in mRSS, and, at the time the study was designed, the patient populations had not been enriched for patients with SSc-associated interstitial lung disease.

Safety results over the 96-week treatment period were consistent with the known safety profile of tocilizumab; infections were the most frequently reported AEs and SAEs, and an increased rate of serious infections was observed after patients transitioned from placebo to tocilizumab. AEs tended to occur more frequently in the first few months after patients transitioned from placebo to tocilizumab but less frequently in longer-term follow-up. Infections were the most frequently reported SAEs in clinical trials of tocilizumab in patients with rheumatoid arthritis (RA).[23 24] Rates of SAEs and serious infections in this study in patients with SSc were approximately five times and eight times higher, respectively, than those reported in patients with RA,[23 24] which is expected given the high morbidity and mortality in patients with SSc.[1] The frequencies of SAEs and serious infections observed in faSScinate are consistent with those in other SSc studies.[25–27] Patients with SSc may be prone to digital ulcers,[1] and complications of digital ulcers occur in 15%

of patients with SSc.[28] The occurrence of two cases of infected digital ulcers and one of osteomyelitis in patients who transitioned from placebo to open-label tocilizumab suggested that tocilizumab may increase infections in patients with SSc-associated digital ulcers, likely over pressure areas such as proximal interphalangeal joints.

The present study had some important limitations. First, all patients received open-label tocilizumab after week 48; therefore, the data collected during the open-label period were uncontrolled. There was a high discontinuation rate. During the open-label period, 7 of the 31 (23%) patients originally assigned to placebo who entered the open-label period and 3 of the 30 (10%) patients originally assigned to tocilizumab who entered the open-label period withdrew from the study. The discontinuation rate from 48 to 96 weeks (16%) was lower than it was in the first 48 weeks of the study (28%). Overall, 63% of patients originally assigned to receive tocilizumab and 55% of patients originally assigned to receive placebo completed the full 96 weeks of treatment. It is likely that patients who completed week 48 and entered the open-label period were less ill or responded better to treatment and perhaps had already experienced more improvement. This selection bias is a common problem associated with open-label, long-term extension studies.[29] Withdrawal of patients who experience AEs leads to the selection of healthier patients, which should be considered when interpreting the longer-term rates of AEs and SAEs. Second, patients with elevated acute-phase reactants were enrolled in this study; therefore, further studies may be needed to investigate the efficacy and safety of tocilizumab in other patient subsets. Third, given the limited numbers of patients with serious infections, analysis of the data to identify potential risk factors, in particular for any interaction of risk factors with tocilizumab, would be underpowered and was not performed. A phase III study with a larger sample size is under way. Last, another limitation is that the study was not designed or powered for formal statistical comparison of the two treatment arms during the open-label period, and formal testing of this exploratory data was not prespecified. For the same reason, a comparison of placebo patients who completed the open-label phase with those in the tocilizumab treatment arm at week 48 is not appropriate. Therefore, although trends can be observed, comparative analyses could not be interpreted in a meaningful way, and formal statistical testing was not feasible.

No disease-modifying therapies have been approved for the treatment of patients with SSc, but some may control symptoms. Treatment options for patients with SSc are largely dependent on the organs affected.[30 31] For example, cyclophosphamide has demonstrated improvement[32] or trends for improvement[33] in lung function in patients with SSc and interstitial lung disease, though its use has been associated with significant toxicity.[30] Similarly, stem cell transplantation has resulted in improvements in skin fibrosis and prevention of lung decline and mortality but is associated with significant costs and risks.[34–36] Methotrexate has demonstrated trends for improvement in skin scores in randomised controlled trials in patients with early SSc.[37 38] Recently, MMF has shown efficacy similar to that of cyclophosphamide for lung and skin fibrosis.[39 40] Tocilizumab may be the first targeted agent to show benefit in the amelioration of skin sclerosis and the prevention of pulmonary decline in patients with SSc.[18]

Overall, the open-label results of the faSScinate study support observations reported from the double-blind period in that the placebo and tocilizumab groups improved similarly when placebo patients were switched to active treatment. Further studies are required to investigate the efficacy and safety of tocilizumab in the treatment of patients with SSc and to determine whether tocilizumab produces significant improvement in skin sclerosis and stabilisation of lung function. A double-blind, phase III randomised controlled trial (NCT02453256) will investigate the efficacy and safety of tocilizumab compared with placebo in a 48-week double-blind period and a 48-week open-label period to further investigate the findings of the phase II faSScinate trial.

In conclusion, together with the results from the first 48 weeks of double-blind treatment,[18] results from the open-label period of the faSScinate trial suggest that treatment with tocilizumab is associated with benefits for skin fibrosis, lung fibrosis and physical function in patients with SSc but increased risk for serious infections. Tocilizumab may be a promising targeted therapy for patients with progressive SSc who have few treatment options.

Author affiliations
[1]University of Michigan Scleroderma Program, Ann Arbor, Michigan, USA
[2]University College London Medical School, London, UK
[3]Genentech, South San Francisco, California, USA
[4]University Medical Center Utrecht, Utrecht, Netherlands
[5]University of Utah, Veterans Affairs Medical Center, Salt Lake City, Utah, USA
[6]University of Liverpool and Aintree University Hospital, Liverpool, UK
[7]Jewish General Hospital, Montreal, Canada
[8]Stanford University School of Medicine and Palo Alto VA Health Care System, Palo Alto, California, USA
[9]University of Tübingen, Tübingen, Germany
[10]University of Connecticut Health Center, Farmington, Connecticut, USA
[11]Paris Descartes University, Paris, France
[12]Schulich School of Medicine and Dentistry, University of Western Ontario, St Joseph's Health Care, London, Canada
[13]University of Lübek and Charité University Hospital, Berlin, Germany
[14]Georgetown University, Washington, DC, USA
[15]Justus-Liebig University Giessen, Kerckhoff Clinic, Bad Nauheim, Germany
[16]Roche Products Ltd, Welwyn Garden City, UK
[17]University of California, Los Angeles, California, USA

Acknowledgements The authors thank Jennifer Adlington, PhD, and Sara Duggan, PhD, for professional writing and editorial assistance in preparing the first draft of the manuscript, on behalf of F Hoffmann-La Roche Ltd.

Contributors All authors were involved in drafting the article or revising it critically for important intellectual content, approved the final draft to be published, and agree be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. DK, CPD and AJ contributed to the conception and design of the study and the acquisition, analysis and interpretation of data. CJFL and YA contributed to the analysis and interpretation of data. JMvL, TMF, MB, LC, GF, SL and VS contributed to acquisition of data. MEA and GR contributed to conception and design of the study and acquisition of data. JEP and LB contributed to acquisition, analysis and interpretation of data. UM-L, HS, JS and DEF contributed to conception and design of the study and analysis and interpretation of data.

Funding This study was funded by Roche. Funding for manuscript preparation was provided by F Hoffmann-La Roche Ltd.

Competing interests DK reports personal fees from Actelion, Boehringer-Ingelheim, Covis, CSL Behring, Corbus, Cytori, EMD Serono, Genentech/Roche, GSK, Inventiva, Medac, Sanofi-Aventis and UCB; grants from BMS, Bayer and Pfizer; stocks in Eicos Sciences, Inc, during the conduct of the study; and personal fees from Astra Zeneca outside the submitted work. CPD reports personal fees from Roche, Actelion, EMD Serono, Sanofi and Boehringer Ingelheim; grants and personal fees from GSK and Inventiva; and grants from CSL Behring during the conduct of the study. CJFL is an employee of Genentech. JMvL reports grants and personal fees from MSD and Genentech and personal fees from BMS, Eli Lilly and Pfizer outside the submitted work. MEA reports funding to Hospital Trust from Roche during the conduct of the study and personal fees from Actelion Pharmaceuticals outside the submitted work. YA has received research support and grants related to the submitted work from BMS, Roche/Genentech, Inventiva, Pfizer and Sanofi; consulting honoraria and personal fees related to the current work from Actelion, Bayer, Boehringer, Roche/Genentech, Galapagos, Inventiva, Medac, Pfizer, Sanofi, Servier and UCB; and personal fees outside the submitted work from Sandoz. JEP reports funding for the current trial by Roche. GR has received lecturer's fees from Roche and Chugai outside the submitted work. UM-L is a speaker and advisor to Roche and Chugai related to the submitted work. HS is an employee of and has non-voting shares in Roche Products Limited. LB is an employee of Roche. JS is an employee of Genentech. AJ is an employee of Genentech, owns stock and options in Roche and owns a patent for subcutaneous tocilizumab. All other authors have no conflicts of interest to disclose.

Patient consent Obtained.

Ethics approval Informed consent forms and other recruitment materials were approved by the Institutional Review Board/Ethics Committee before study initiation. The study was conducted in compliance with the International Conference on Harmonisation for Good Clinical Practice Guidelines and the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Nikpour M, Stevens WM, Herrick AL, *et al*. Epidemiology of systemic sclerosis. *Best Pract Res Clin Rheumatol* 2010;24:857–69.
2 Denton CP. Systemic sclerosis: from pathogenesis to targeted therapy. *Clin Exp Rheumatol* 2015;33(4 Suppl 92):S3–7.
3 Denton CP, Khanna D. Systemic sclerosis. *The Lancet* 2017;S0140-6736(17)30933-9. [Epub ahead of print].
4 Ioannidis JP, Vlachoyiannopoulos PG, Haidich AB, *et al*. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. *Am J Med* 2005;118:2–10.
5 Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis* 2007;66:940–4.
6 Khanna D, Distler JHW, Sandner P, *et al*. Emerging strategies for treatment of systemic sclerosis. *J Scleroderma Relat Disord* 2016;1:186–93.
7 Muangchant C, Pope JE. The significance of interleukin-6 and C-reactive protein in systemic sclerosis: a systematic literature review. *Clin Exp Rheumatol* 2013;31(2 Suppl 76):122–34.
8 Muangchan C, Pope JE. Interleukin 6 in systemic sclerosis and potential implications for targeted therapy. *J Rheumatol* 2012;39:1120–4.
9 Koch AE, Kronfeld-Harrington LB, Szekanecz Z, *et al*. In situ expression of cytokines and cellular adhesion molecules in the skin of patients with systemic sclerosis. Their role in early and late disease. *Pathobiology* 1993;61:239–46.
10 Khan K, Xu S, Nihtyanova S, *et al*. Clinical and pathological significance of interleukin 6 overexpression in systemic sclerosis. *Ann Rheum Dis* 2012;71:1235–42.
11 De Lauretis A, Sestini P, Pantelidis P, *et al*. Serum interleukin 6 is predictive of early functional decline and mortality in interstitial lung disease associated with systemic sclerosis. *J Rheumatol* 2013;40:435–46.
12 Sato S, Hasegawa M, Takehara K. Serum levels of interleukin-6 and interleukin-10 correlate with total skin thickness score in patients with systemic sclerosis. *J Dermatol Sci* 2001;27:140–6.
13 Matsushita T, Hasegawa M, Hamaguchi Y, *et al*. Longitudinal analysis of serum cytokine concentrations in systemic sclerosis: association of interleukin 12 elevation with spontaneous regression of skin sclerosis. *J Rheumatol* 2006;33:275–84.
14 Muangchan C, Harding S, Khimdas S, *et al*. Association of C-reactive protein with high disease activity in systemic sclerosis: results from the Canadian Scleroderma Research Group. *Arthritis Care Res* 2012;64:1405–14.
15 Genentech Inc. *Actemra (tocilizumab) injection for intravenous infusion*. South San Francisco,CA: Genentech, Inc, 2017.
16 Shima Y, Kuwahara Y, Murota H, *et al*. The skin of patients with systemic sclerosis softened during the treatment with anti-IL-6 receptor antibody tocilizumab. *Rheumatology* 2010;49:2408–12.
17 Elhai M, Meunier M, Matucci-Cerinic M, *et al*. Outcomes of patients with systemic sclerosis-associated polyarthritis and myopathy treated with tocilizumab or abatacept: a EUSTAR observational study. *Ann Rheum Dis* 2013;72:1217–20.
18 Khanna D, Denton CP, Jahreis A, *et al*. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. *Lancet* 2016;387:2630–40.
19 van den Hoogen F, Khanna D, Fransen J, *et al*. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis* 2013;72:1747–55.
20 Khanna D, Furst DE, Hays RD, *et al*. Minimally important difference in diffuse systemic sclerosis: results from the D-penicillamine study. *Ann Rheum Dis* 2006;65:1325–9.
21 Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case ofbinomial. *Biometrika* 1934;26:404–13.
22 Distler O, Distler JH. Tocilizumab for systemic sclerosis: implications for future trials. *Lancet* 2016;387:2580–1.
23 Schiff MH, Kremer JM, Jahreis A, *et al*. Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther* 2011;13:R141.
24 Genovese MC, Rubbert-Roth A, Smolen JS, *et al*. Longterm safety and efficacy of tocilizumab in patients with rheumatoid arthritis: a cumulative analysis of up to 4.6 years of exposure. *J Rheumatol* 2013;40:768–80.
25 Denton CP, Merkel PA, Furst DE, *et al*. Recombinant human anti-transforming growth factor beta1 antibody therapy in systemic sclerosis: a multicenter, randomized, placebo-controlled phase I/II trial of CAT-192. *Arthritis Rheum* 2007;56:323–33.
26 Spiera RF, Gordon JK, Mersten JN, *et al*. Imatinib mesylate (Gleevec) in the treatment of diffuse cutaneous systemic sclerosis: results of a 1-year, phase IIa, single-arm, open-label clinical trial. *Ann Rheum Dis* 2011;70:1003–9.
27 Foocharoen C, Siriphannon Y, Mahakkanukrauh A, *et al*. Incidence rate and causes of infection in Thai systemic sclerosis patients. *Int J Rheum Dis* 2012;15:277–83.
28 Muangchan C, Baron M, Pope J. The 15% rule in scleroderma: the frequency of severe organ complications in systemic sclerosis. a systematic review. *J Rheumatol* 2013;40:1545–56.
29 Buch MH, Aletaha D, Emery P, *et al*. Reporting of long-term extension studies: lack of consistency calls for consensus. *Ann Rheum Dis* 2011;70:886–90.
30 Kowal-Bielecka O, Landewé R, Avouac J, *et al*. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis* 2009;68:620–8.
31 Nagaraja V, Denton CP, Khanna D. Old medications and new targeted therapies in systemic sclerosis. *Rheumatology* 2015;54:1944–53.
32 Tashkin DP, Elashoff R, Clements PJ, *et al*. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006;354:2655–66.
33 Hoyles RK, Ellis RW, Wellsbury J, *et al*. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum* 2006;54:3962–70.
34 Burt RK, Shah SJ, Dill K, *et al*. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. *Lancet* 2011;378:498–506.
35 van Laar JM, Farge D, Sont JK, *et al*. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA* 2014;311:2490–8.
36 McSweeney PA, Nash RA, Sullivan KM, *et al*. High-dose immunosuppressive therapy for severe systemic sclerosis: initial outcomes. *Blood* 2002;100:1602–10.
37 Pope JE, Bellamy N, Seibold JR, *et al*. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum* 2001;44:1351–8.
38 van den Hoogen FH, Boerbooms AM, Swaak AJ, *et al*. Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial. *Br J Rheumatol* 1996;35:364–72.
39 Tashkin DP, Roth MD, Clements PJ, *et al*. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *Lancet Respir Med* 2016;4:708–19.
40 Namas R, Tashkin DP, Furst DE, *et al*. Efficacy of mycophenolate mofetil and oral cyclophosphamide on skin thickness: Post-hoc analyses from the Scleroderma Lung Study I and II. *Arthritis Care Res* 2017.

OPEN ACCESS

EXTENDED REPORT

Evaluation of the change in structural radiographic sacroiliac joint damage after 2 years of etanercept therapy (EMBARK trial) in comparison to a contemporary control cohort (DESIR cohort) in recent onset axial spondyloarthritis

Maxime Dougados,[1] Walter P Maksymowych,[2] Robert B M Landewé,[3] Anna Moltó,[1] Pascal Claudepierre,[4] Manouk de Hooge,[5] Robert G Lambert,[6] Randi Bonin,[7] Jack F Bukowski,[7] Heather E Jones,[8] Isabelle Logeart,[9] Ron Pedersen,[10] Annette Szumski,[11] Bonnie Vlahos,[7] Désirée van der Heijde[5]

Handling editor Tore K Kvien
For numbered affiliations see end of article.

Correspondence to
Professor Maxime Dougados, Paris Descartes University, Rheumatology Department, Cochin Hospital, Assistance Publique - Hôpitaux de Paris, INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, France;
maxime.dougados@aphp.fr

Received 30 June 2017
Revised 1 September 2017
Accepted 19 September 2017
Published Online First
29 September 2017

ABSTRACT

Objective To compare 2 years of radiographic sacroiliac joint (SIJ) changes in patients with recent onset axial spondyloarthritis (axSpA) receiving etanercept in a clinical trial (EMBARK) to similar patients not receiving biologics in a cohort study (DESIR).

Methods Endpoints were changes at week 104 per the modified New York (mNY) grading system in total SIJ score (primary endpoint) and net percentage of patients with progression defined three ways. Treatment effect was analysed with and without adjustment for baseline covariates.

Results At 104 weeks, total SIJ score improved in the etanercept group (n=154, adjusted least-squares mean change: −0.14) and worsened in the control group (n=182, change: 0.08). The adjusted difference between groups (etanercept minus control) was −0.22 (95% CI −0.38 to −0.06), p=0.008. The net percentage of patients with progression was significantly lower in the etanercept versus the control group for two of three binary endpoints: −1.9% versus 1.6% (adjusted difference for etanercept minus control: −4.7%,95% CI −9.9 to 0.5, p=0.07) for change in mNY criteria; −1.9% versus 7.8% (adjusted difference: −18.2%,95% CI −30.9 to −5.6, p=0.005) for change ≥1 grade in ≥1 SIJ; and −0.6% versus 6.7% (adjusted difference: −16.4%,95% CI −27.9 to −5.0, p=0.005) for change ≥1 grade in ≥1 SIJ, with shift from 0 to 1 or 1 to 0 considered no change.

Conclusion Despite the slow radiographic SIJ progression rate over 2 years in axSpA, this study suggests a lower rate of progression in the SIJ with etanercept than without anti-tumour necrosis factor therapy.

Trial registration numbers NCT01258738,NCT01648907; Post-results.

To cite: Dougados M, Maksymowych WP, Landewé RBM, *et al*. *Ann Rheum Dis* 2018;**77**:221–227.

INTRODUCTION

The most frequently observed symptoms in spondyloarthritis (SpA) are axial.[1 2] The various criteria for SpA (eg, Amor, European Spondyloarthropathy Study Group and, more recently, the Assessment of SpondyloArthritis international Society (ASAS) criteria) enable classification of patients in the absence of radiographic structural damage, that is, non-radiographic axial SpA (nr-axSpA).[3–7] In patients with an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs) with radiographic (r-) or nr-axSpA, anti-tumour necrosis factor (TNF) agents have demonstrated a beneficial effect on symptoms,[8–11] but their structural effect is still unclear.[12–17]

Structural evaluation of axSpA can be performed using conventional radiographs or MRI at the spine or pelvic level. Radiographic axSpA studies have focused on the spine using a radiography scoring system, and data suggest that a structural effect either does not exist[18 19] or requires studies >2 years to be observed.[20 21] Questions exist about the risk of future structural damage, particularly at the sacroiliac joint (SIJ) level, in patients with nr-axSpA. Approximately 10% of patients with nr-axSpA develop SIJ radiographic damage within 2 years and 60% within 10 years.[22–24]

The conventional method for assessing SIJ structural damage on radiography is the modified New York (mNY) grading system, consisting of a semiquantitative scale from 0 (normal) to 4 (total ankylosis).[2] However, this method has been criticised because of its poor reliability.[25] Moreover, this grading system has no accepted method to evaluate change in radiographic damage except the categorisation of a patient as having either nr-axSpA or r-axSpA: r-axSpA is considered to be at least grade 2 bilaterally or at least grade 3 unilaterally. Alternative outcome measures appear to be more sensitive, such as change in the total score over time, and percentage of patients with a change of at least one grade in at least one SIJ.[24 26]

Ideally, a long-term controlled clinical trial would address the structural impact of long-term treatment. Additionally, a robust study should include both a treatment and a control group. However, it is not possible to conduct a study of sufficient length, that is, at least 2 years, with a placebo control.[21]

Another option is to compare a treatment cohort from one study to a control cohort in another study. This technique has been used to

evaluate the structural changes observed at the spine level in r-axSpA in patients receiving an anti-TNF. These patients have been compared with a control group consisting of patients in a study evaluating the natural history of r-axSpA, the OASIS cohort.[13 16 17 27]

All of these considerations prompted us to conduct a study in patients with early axSpA aimed at evaluating the radiographic changes in the SIJ observed after 2 years of etanercept therapy in patients enrolled in a clinical trial (EMBARK) compared with usual care in patients enrolled in an observational cohort (DESIR).

PATIENTS AND METHODS

Details of the EMBARK trial have been described previously.[8 28 29] All patients fulfilled the ASAS criteria for axSpA, but based on a central reading procedure, none of them met the mNY criteria for radiographic status. Patients were aged ≥18 and <50 years with symptoms for >3 months but <5 years, had a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥4 of 10, and had symptoms of back pain with an inadequate response to ≥2 NSAIDs. After a 12-week, double-blind, placebo-controlled period, all patients received etanercept 50 mg once weekly during a 92-week open-label period.

The DESIR cohort has been described in detail.[23] The study included patients aged >18 and <50 years with inflammatory back pain for >3 months but <3 years, suggestive of axSpA according to the treating rheumatologist. Patients with a history of treatment with any biological therapy were excluded.

The present analysis included the patients from the EMBARK trial with available baseline and 2-year pelvic radiographs, and patients from the DESIR cohort who met the ASAS criteria for axSpA, did not receive any biological therapy during the first two years of follow-up and had baseline and 2-year pelvic radiographs.

Grading of radiographic sacroiliitis

Radiographic sacroiliitis was graded using the 0–4 grade scale for the left and right SIJ from the mNY grading system.[2] The scale is provided below:

- Grade 0: normal.
- Grade 1: suspicious changes.
- Grade 2: minimal abnormality—small localised areas with erosion or sclerosis, without alteration in the joint width.
- Grade 3: unequivocal abnormality—moderate or advanced sacroiliitis with one or more of erosions, evidence of sclerosis, widening, narrowing or partial ankylosis.
- Grade 4: severe abnormality—total ankylosis.

Reading the radiographs

The SIJ radiographs from the DESIR and EMBARK cohorts were anonymised so that the readers were unaware of the chronology of the films and the original patient cohort. The three trained and experienced readers, who were not readers used for screening in either DESIR or EMBARK, met via videoconference for a calibration session prior to the start of this analysis. They graded each joint at each time point, with a scale from 0 to 4 per the mNY grading system.

Assessments

The primary endpoint was change in total SIJ score at week 104. Total SIJ score was obtained by adding the scores of both SIJs according to the mNY grading system (0–4 per SIJ, range from 0 to 8); thus the change could range from −8 to +8. For this endpoint, the mean change of the three readers' values was used. Three binary endpoints were also evaluated: (1) proportion of patients switching from mNY criteria negative at baseline to mNY criteria positive at week 104 and the proportion of patients switching from mNY criteria positive at baseline to mNY criteria negative at week 104 (based on the central reading for the current analysis); and (2) proportion of patients with change (improvement or worsening in SIJ score of ≥1) in at least one SIJ. The third binary endpoint excluded minimal or doubtful changes (changes from normal appearance (grade 0) to 'suspicious' abnormalities of the SIJ (grade 1)) from the improved or worsened categories: proportion of patients with change (improvement or worsening in SIJ score of ≥1) in at least one SIJ, with a shift from 0 to 1 (in the worsened joint) or from 1 to 0 (in the improved joint) considered no change. For these binary endpoints, improvement or worsening was assigned only if at least two of the three readers agreed on the direction of change.

Other collected data

In both studies, patient demographics and clinical outcome measures of disease activity were collected at baseline and throughout the duration of the follow-up. The baseline SIJ MRI evaluating the presence of inflammation according to the Spondyloarthritis Research Consortium of Canada (SPARCC) method[30] was assessed separately in EMBARK and DESIR using a central reading procedure previously described.[29 31] A score ≥2 was considered an indicator of SIJ inflammation on MRI.[32]

Statistical analysis

This analysis included the completer population, defined as having pelvic radiographs available at baseline and 2 years. Baseline characteristics were analysed using either the Wilcoxon rank-sum or the Mantel-Haenszel χ^2 test. The radiographic analyses were conducted without covariates (unadjusted analysis) and also with the following covariates as potential baseline confounders (adjusted analysis): sex, symptom duration, smoking status, human leucocyte antigen (HLA)-B27 status, Ankylosing Spondylitis Disease Activity Score (ASDAS) with C reactive protein, SPARCC MRI SIJ score and total SIJ score based on the mNY grading system. One-way analysis of variance was used to compare study cohorts for the unadjusted difference, and analysis of covariance was used for the adjusted difference.

The a priori primary outcome measure was the absolute change in total SIJ score adjusted for baseline covariates. For each of the three binary endpoints, the percentage of patients with disease progression (worsening) and the percentage of patients with disease regression (improvement) was determined per group. Additionally, the net percentage of patients with progression was defined as the number of patients with worsening minus the number of patients with improvement, divided by the total study population. The between-group difference in the net percentage of patients with progression was reported for each of the three binary endpoints. A cumulative probability plot was generated to compare the change in SIJ radiography score from baseline to week 104 for the control and etanercept cohorts. Change was defined as the average change of the three readers.

RESULTS

The EMBARK trial included 225 randomised patients; a complete data set was available for 162 patients. The DESIR cohort study enrolled 708 patients; 506 of these patients did not receive a biological therapy during the 2 years of follow-up, 283 of these 506 patients fulfilled the ASAS criteria for axSpA and

Table 1 Demographics and baseline disease characteristics

	Control (DESIR) n=193	Etanercept (EMBARK) n=162	p Value
Age, years	32.2 (7.0)	31.8 (7.7)	0.47*
Male, n/N (%)	100/193 (51.8)	106/162 (65.4)	0.01†
Symptom duration, years	1.7 (1.0)	2.4 (1.8)	<0.001*
Current smoker, n/N (%)	70/192 (36.5)	37/162 (22.8)	0.006†
HLA-B27(+), n/N (%)	162/193 (83.9)	113/156 (72.4)	0.009†
BASDAI (0–10)	3.6 (1.9)	5.9 (1.8)	<0.001*
ASDAS	2.2 (0.9)	3.0 (1.0)	<0.001*
BASFI (0–10 cm VAS)	2.2 (2.0)	4.0 (2.4)	<0.001*
CRP, mg/L	5.4 (7.5)	6.9 (11.2)	0.06*
SPARCC MRI SIJ score (0–72)	5.8 (9.5)	8.4 (11.0)	<0.001*
SPARCC MRI SIJ score ≥2, n/N (%)	78/191 (40.8)	95/159 (59.7)	<0.001†
Total SIJ score (mNY grade 0–8)	1.9 (1.6)	1.5 (1.2)	0.03*
SIJ score met mNY criteria, n/N (%)	39/193 (20.2)	19/162 (11.7)	0.03†

Values are mean (SD) unless otherwise noted.
*Wilcoxon rank-sum.
†Mantel-Haenszel.
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; HLA, human leucocyte antigen; mNY, modified New York; SIJ, sacroiliac joint; SPARCC, Spondyloarthritis Research Consortium of Canada; VAS, visual analogue scale.

193 had both baseline and 2-year pelvic radiographs available and qualified for this study. Demographics and baseline disease characteristics are provided in table 1.

At baseline, several differences existed between the groups: a higher proportion of males and longer disease duration in the etanercept group, and a higher proportion of smokers and HLA-B27-positive patients in the control group. Because all EMBARK patients were eligible for initiation of anti-TNF therapy and none of the DESIR cohort received an anti-TNF during the 2-year follow-up period, it is not surprising that the disease activity markers of BASDAI, ASDAS and SPARCC MRI SIJ inflammation were significantly higher in the etanercept group at baseline. Conversely, total SIJ score was slightly but significantly higher in the control group.

After 104 weeks, there was a slightly positive change (worsening) in the total SIJ score for the control group versus a slightly negative change (improvement) in the etanercept group in the adjusted analysis (least-squares mean change: 0.08 (95% CI −0.04 to 0.20) vs −0.14 (95% CI −0.26 to −0.01)). The adjusted between-group difference in change (etanercept − control) was significant: −0.22 (95% CI −0.38 to −0.06, p=0.008); the unadjusted between-group difference was not significant: −0.11 (95% CI −0.25 to 0.02, p=0.10).

Figure 1 presents the cumulative probability plot for the change in SIJ radiography score over 104 weeks. The control cohort trended towards worsening, with more patients having a positive score. In contrast, the etanercept cohort trended towards improvement, with more patients having a negative score.

The observed radiographic changes from baseline to week 104 are shown in table 2. For change in mNY criteria, the net percentage of patients with progression was lower in the etanercept versus the control group; however, the difference between the groups was not statistically significant: −1.9% versus 1.6% (adjusted difference for etanercept minus control: −4.7%, 95% CI −9.9 to 0.5, p=0.07). For the other two binary endpoints, the net percentage of patients with progression was significantly lower in the etanercept versus the control group: −1.9% versus 7.8% (adjusted difference: −18.2%, 95% CI −30.9 to −5.6, p=0.005) for change ≥1 grade in at least one SIJ; and −0.6% versus 6.7% (adjusted difference: −16.4%, 95% CI −27.9 to −5.0, p=0.005) for change ≥1 grade in at least one SIJ, with shift from 0 to 1 or 1 to 0 considered no change.

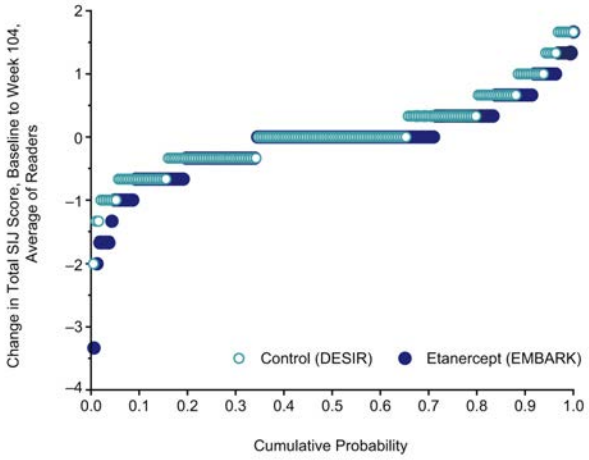


Figure 1 Cumulative probability of change in sacroiliac joint (SIJ) radiography score from baseline to week 104 for the control and etanercept cohorts, average of the readers.

Figure 2 presents the net percentage of patients with progression in the two study groups for the three binary endpoints.

DISCUSSION

This study supports the existence of a small structural effect of anti-TNF therapy in the SIJ using plain pelvic radiographs as the primary assessment tool and the mNY grading system as the outcome measure. It also confirms the relatively slow rate of radiographic progression in the SIJ in terms of shifting from non-radiographic to radiographic status according to the mNY criteria over a 2-year period.

An assessment of 2-year SIJ radiographic progression in early axSpA was also conducted in the German Spondyloarthritis Inception Cohort (GESPIC), a cohort comparable to DESIR.[24] A similar rate of SIJ radiographic progression was observed, with a mean change in the SIJ score of 0.07 (95% CI −0.05 to 0.19) and 0.09 (95% CI −0.03 to 0.21) for the left and right SIJ, respectively.[24] Moreover, in the GESPIC cohort, after 2 years, 11 of the 95 patients with nr-axSpA at baseline met the mNY criteria for r-axSpA (ie, worsened).[24] Additionally, 3 of the 115 patients with r-axSpA at baseline did not fulfil the mNY criteria at year 2 (ie, improved).[24] Calculating the net rate of progression for the full study population results in a rate of 3.8% ((11 − 3)/(95+115)). This is similar to the data observed in the present study for the DESIR patients (control group), with a net progression rate of 1.6% (95% CI −1.3% to 4.4%). The slight difference between the two studies may be due to chance or may be explained by different patient phenotypes, in particular, the proportion of patients with SIJ inflammation on MRI (greater in the GESPIC cohort than in this DESIR subgroup).

When considering an outcome parameter based on a semiquantitative variable (score 0–4 per side), including different types of damage, collected in the left and right joints, some concerns may

Table 2 Observed radiographic changes from baseline to week 104

Endpoint	Cohort	Improved n/N (%)	Worsened n/N (%)	Net % patients with progression,*† unadjusted (95% CI)	Between-group differences in net % patients with progression, Etanercept—Control (95% CI)	
					Unadjusted analysis	Adjusted analysis‡
Δ in mNY criteria	Control Etanercept	3/193 (1.6) 4/162 (2.5)	6/193 (3.1) 1/162 (0.6)	1.6% (−1.3 to 4.4) −1.9% (−4.9 to 1.2)	−3.4% (−7.6 to 0.8) p=0.11	−4.7% (−9.9 to 0.5) p=0.07
Δ ≥1 grade in ≥1 SIJ	Control Etanercept	21/193 (10.9) 19/162 (11.7)	36/193 (18.7) 16/162 (9.9)	7.8% (0.6 to 15.0) −1.9% (−9.7 to 6.0)	−9.6% (−20.3 to 1.0) p=0.08	−18.2% (−30.9 to −5.6) p=0.005
Δ ≥1 grade in ≥1 SIJ; shift from 0 to 1 or 1 to 0 considered no Δ	Control Etanercept	16/193 (8.3) 15/162 (9.3)	29/193 (15.0) 14/162 (8.6)	6.7% (0.3 to 13.2) −0.6% (−7.6 to 6.4)	−7.4% (−16.9 to 2.2) p=0.13	−16.4% (−27.9 to −5.0) p=0.005

Based on two of three readers assigning same category; otherwise considered no change.
Some patients started with lowest possible score and could not improve.
*Net % patients with progression=number of patients with worsening minus the number of patients with improvement, divided by the study population.
†One-way analysis of variance.
‡Adjusted for these covariates at baseline: sex, symptom duration, smoking status, human leucocyte antigen-B27 status, Ankylosing Spondylitis Disease Activity Score, Spondyloarthritis Research Consortium of Canada MRI SIJ score and SIJ mNY grade.
Δ, change; mNY, modified New York; SIJ, sacroiliac joint.

be raised. Semiquantitative scores may not be translated into continuous scores without consideration since it is unknown if the steps in the semiquantitative score are equidistant. While this is a technical limitation of our study, this approach is frequently used in medicine in general and in rheumatology in particular, and we do not believe that it has influenced the results.

Dichotomisation is a frequently used technique to overcome scaling issues related to semiquantitative scores and interpretational concerns from continuous scores. Dichotomisation also assists in the analysis of non-normally distributed data. It is tempting for clinicians to interpret radiographic change scores as dichotomies (those that progress vs those that do not; those that have nr-axSpA vs those that have r-axSpA). However, dichotomisation is a simplification of the truth because it largely ignores measurement error. Measuring radiographic change in patients with SpA is a challenge since the true change ('the signal') in a patient is usually outweighed by spurious change ('the noise') due to differences in technique and inherent rater variability. An observed difference between groups is only credible if the scores have been obtained under unbiased conditions and all possible directions of change have been considered.

'Net percentage of patients with progression' is a concept we explored to combine the advantages of dichotomisation ('progressor' or 'non-progressor') while preserving the option of adjusting for measurement error. It is an artificial concept in terms of interpretation since it appears possible in a single patient to adjust the true signal for the noise of measurement error, which is not the case. Net percentage of patients with progression should be interpreted at the group level. Although more patients had disease progression than disease regression overall, this difference cannot be translated to an individual patient. Therefore, the concept does not elementarily differ from the comparison of group means.

Another potential issue when using the mNY grading system as an outcome measure is that two concepts are mixed: repair (sclerosis) and destruction (joint erosion). One patient may have a change in sclerosis and another may have a change in erosion, and the grade change could be the same. Additionally, the results can vary between readers since the inter-reader reliability of this approach is known to be quite poor.[25 26] In EMBARK there was a greater proportion of patients with regression than progression, resulting in a negative parameter estimate for progression rate. This may be due to measurement error or a true repair process with a reduction in erosions.

The switch from a continuous or semiquantitative to a binary variable (progression yes/no) necessitates choosing a cut-off. Because the conventional yet arbitrary mNY criteria distinguish between radiographic and non-radiographic status, it was tempting to use these to describe a patient at a particular time point and to estimate the natural disease history. It was also tempting to present the results in a simpler, more understandable manner, such as change of ≥1 grade in ≥1 SIJ. We used the approach proposed by the GESPIC investigators. However, because of the difficulty in distinguishing a grade 0 from a grade 1, we modified this system by excluding the change from grade 0 to grade 1 for the worsened joint or from grade 1 to 0 for the improved joint.[26]

These results suggest a significant structural effect of etanercept in the SIJ. The treatment group was not compared with a control group within a prospective randomised controlled trial; rather, it was compared with a contemporary cohort of patients. Consequently, the baseline characteristics differed between the two groups, particularly the disease activity. All patients in EMBARK were eligible for anti-TNF therapy; the DESIR patients in this study did not receive biological therapy. Therefore, we adjusted for covariates that may affect radiographic progression.[24 26 33]

To our knowledge, this is the first study to evaluate the anti-TNF structural effect in the SIJ using plain pelvic radiography as the assessment tool and the mNY grading system as the scoring method. These results should be considered within the context of the literature. Previous studies of radiographic progression in axSpA evaluated the spine since structural damage in the spine correlates with functional impairment. However, study results suggest that a longer period of evaluation is needed to observe a structural anti-TNF effect in the spine.[13 16 17 34 35] The clinical relevance of our study may be more difficult to interpret since the correlation between a change in radiographic SIJ damage and the functional capacity of a patient is usually considered poor. Future studies are needed to better evaluate the predictive validity of this outcome measure.

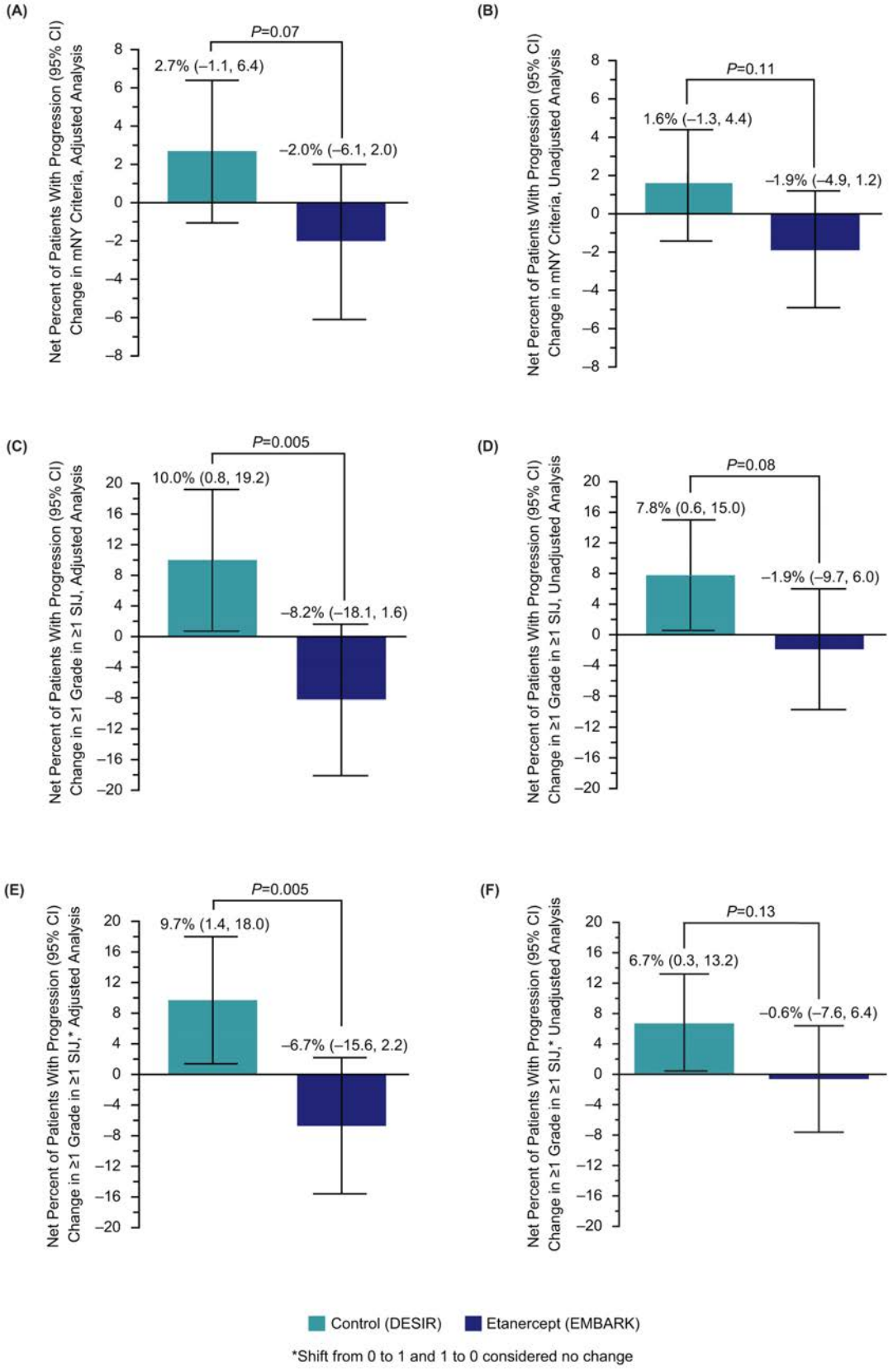


Figure 2 Net percent of patients with progression (number of patients with worsening minus the number of patients with improvement, divided by the study population) from baseline to week 104 in each study group for the three binary endpoints: (A) change in modified New York (mNY) criteria, adjusted analysis and (B) unadjusted analysis; (C) change of ≥1 grade in ≥1 sacroiliac joint (SIJ), adjusted analysis and (D) unadjusted analysis; and (E) change of ≥1 grade in ≥1 SIJ with shift from 0 to 1 and from 1 to 0 considered no change, adjusted analysis and (F) unadjusted analysis.

Our study has several strengths. First, both study cohorts had a large sample size. Second, the scoring methodology was designed to avoid and adjust for bias, that is, the three independent, trained readers were unaware of the chronology of the radiographs and the patient cohort. Third, the study included a control group. Even though both cohorts were not randomised as a whole, the control group was an appropriate comparison for the etanercept group.

These results further support a structural anti-TNF effect in the SIJ.[36] The data are promising, but additional studies are needed to confirm the validity of these outcome measures and to evaluate the structural effect of various therapies in the SIJ using advanced imaging techniques.

Author affiliations
[1]Paris Descartes University, Rheumatology Department, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, France
[2]Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
[3]Amsterdam Rheumatology and Immunology Center, Amsterdam, Netherlands
[4]Universite Paris Est Creteil, EA 7379 – EpidermE, AP-HP, Service de Rhumatologie, Hopital Henri Mondor, Creteil, France
[5]Leiden University Medical Center, Leiden, Netherlands
[6]Department of Radiology and Diagnostic Imaging, University of Alberta, Edmonton, Alberta, Canada
[7]Clinical Affairs, Pfizer, Collegeville, Pennsylvania, USA
[8]Medical Affairs, Pfizer, Collegeville, Pennsylvania, USA
[9]Pfizer France, Paris, France
[10]Department of Biostatistics, Pfizer, Collegeville, USA
[11]Biostatistics, inVentiv Health, Princeton, New Jersey, USA

Acknowledgements The authors thank all patients who participated in this study, as well as the investigators and medical staff at all of the participating centres. This paper is based on work that was previously presented at the 2017 Annual Meeting of the European League Against Rheumatism (EULAR); 14-17 June 2017; Madrid, Spain; and was published as a conference abstract: Dougados M, *et al* Ann Rheum Dis. 2017;76:350-1.

Contributors Study conception or design: MD, WPM, RL, DvdH, JFB, HJ, IL, RP, AS. Acquisition of data: MD, WPM, RL, DvdH, AM, PC, MdH, RGL, RB. Analysis or interpretation of data: MD, WPM, RL, DvdH, AM, PC, MdH, RGL, RB, JFB, HJ, IL, RP, AS, BV. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. All authors agree to be accountable for all aspects of the work.

Funding The EMBARK trial was funded by Pfizer. The DESIR cohort is supported by unrestricted grants from the French Society of Rheumatology and Pfizer. Medical writing support was provided by Jennica Lewis, PharmD, CMPP, of Engage Scientific Solutions and was funded by Pfizer.

Competing interests MD reports grants and personal fees from Pfizer, AbbVie, UCB, Merck, Lilly, Janssen and Novartis during the conduct of the study. WPM reports grants and personal fees from AbbVie and Pfizer, personal fees from Janssen, Lilly, Novartis, Merck and UCB outside the submitted work. RGL reports personal fees from AbbVie and BioClinica outside the submitted work. JFB, HJ, IL, RP and BV are employees of, and own stock in Pfizer. RB was an employee of Pfizer at the time the article was written. AS is an employee of inVentiv Health and was contracted by Pfizer to provide statistical support for the development of this paper. DvdH reports personal fees from AbbVie, Amgen, Astellas, AstraZeneca, Bristol Meyers Squibb, Boehringer Ingelheim, Celgene, Daiichi, Galapagos,Glaxo-Smith-Kline, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda and UCB outside the submitted work; and is director of Imaging Rheumatology BV. RL, AM, PC and MdH have no competing interests to declare.

Ethics approval EMBARK: The institutional review board or independent ethics committee at each participating centre reviewed and approved all consent forms and the study protocol; DESIR: Ile de France III Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Rudwaleit M, van der Heijde D, Landewé R, *et al*. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011;70:25–31.
2 Sieper J, Rudwaleit M, Baraliakos X, *et al*. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009;68 (Suppl 2):1–ii44.
3 Akgul O, Ozgocmen S. Classification criteria for spondyloarthropathies. *World J Orthop* 2011;2:107–15.
4 Dougados M, van der Linden S, Juhlin R, *et al*. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991;34:1218–27.
5 Rudwaleit M, Landewé R, van der Heijde D, *et al*. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009;68:770–6.
6 Rudwaleit M, van der Heijde D, Landewé R, *et al*. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777–83.
7 Amor B, Dougados M, Mijiyawa M. [Criteria of the classification of spondylarthropathies]. *Rev Rhum Mal Osteoartic* 1990;57:85–9.
8 Maksymowych WP, Dougados M, van der Heijde D, *et al*. Clinical and MRI responses to etanercept in early non-radiographic axial spondyloarthritis: 48-week results from the EMBARK study. *Ann Rheum Dis* 2016;75:1328–35.
9 Braun J, Brandt J, Listing J, *et al*. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet* 2002;359:1187–93.
10 Baraliakos X, Haibel H, Fritz C, *et al*. Long-term outcome of patients with active ankylosing spondylitis with etanercept-sustained efficacy and safety after seven years. *Arthritis Res Ther* 2013;15:R67.
11 van der Heijde D, Kivitz A, Schiff MH, *et al*. ATLAS Study Group. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006;54:2136–46.
12 Baraliakos X, Listing J, Brandt J, *et al*. Radiographic progression in patients with ankylosing spondylitis after 4 yrs of treatment with the anti-TNF-alpha antibody infliximab. *Rheumatology* 2007;46:1450–3.
13 van der Heijde D, Salonen D, Weissman BN, *et al*. Canadian (M03-606) study group, ATLAS study group. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. *Arthritis Res Ther* 2009;11:R127.
14 Osman MS, Maksymowych WP. An update on the use of tumor necrosis factor alpha inhibitors in the treatment of ankylosing spondylitis. *Expert Rev Clin Immunol* 2017;13:125–31.
15 Song IH, Hermann KG, Haibel H, *et al*. Inflammatory and fatty lesions in the spine and sacroiliac joints on whole-body MRI in early axial spondyloarthritis-3-Year data of the ESTHER trial. *Semin Arthritis Rheum* 2016;45:404–10.
16 van der Heijde D, Landewé R, Einstein S, *et al*. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. *Arthritis Rheum* 2008;58:1324–31.
17 van der Heijde D, Landewé R, Baraliakos X, *et al*. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. *Arthritis Rheum* 2008;58:3063–70.
18 Ramiro S, van Tubergen A, Stolwijk C, *et al*. Scoring radiographic progression in ankylosing spondylitis: should we use the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) or the Radiographic Ankylosing Spondylitis Spinal Score (RASSS)? *Arthritis Res Ther* 2013;15:R14.
19 Maksymowych WP. Controversies in conventional radiography in spondyloarthritis. *Best Pract Res Clin Rheumatol* 2012;26:839–52.
20 Poddubnyy D, Protopopov M, Haibel H, *et al*. High disease activity according to the Ankylosing Spondylitis Disease Activity Score is associated with accelerated radiographic spinal progression in patients with early axial spondyloarthritis: results from the GErman SPondyloarthritis Inception Cohort. *Ann Rheum Dis* 2016;75:2114–8.
21 van der Heijde D, Landewé R, van der Linden S. How should treatment effect on spinal radiographic progression in patients with ankylosing spondylitis be measured? *Arthritis Rheum* 2005;52:1979–85.
22 Poddubnyy D, Brandt H, Vahldiek J, *et al*. The frequency of non-radiographic axial spondyloarthritis in relation to symptom duration in patients referred because of chronic back pain: results from the Berlin early spondyloarthritis clinic. *Ann Rheum Dis* 2012;71:1998–2001.
23 Dougados M, Etcheto A, Molto A, *et al*. DESIR cohort. Clinical presentation of patients suffering from recent onset chronic inflammatory back pain suggestive of spondyloarthritis: The DESIR cohort. *Joint Bone Spine* 2015;82:345–51.
24 Poddubnyy D, Rudwaleit M, Haibel H, *et al*. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. *Ann Rheum Dis* 2011;70:1369–74.

25 van den Berg R, Lenczner G, Feydy A, *et al*. Agreement between clinical practice and trained central reading in reading of sacroiliac joints on plain pelvic radiographs. Results from the DESIR cohort. *Arthritis Rheumatol* 2014;66:2403–11.
26 Dougados M, Demattei C, van den Berg R, *et al*. Rate and Predisposing Factors for Sacroiliac Joint Radiographic Progression After a Two-Year Follow-up Period in Recent-Onset Spondyloarthritis. *Arthritis Rheumatol* 2016;68:1904–13.
27 Ramiro S, Stolwijk C, van Tubergen A, *et al*. Evolution of radiographic damage in ankylosing spondylitis: a 12 year prospective follow-up of the OASIS study. *Ann Rheum Dis* 2015;74:52–9.
28 Dougados M, van der Heijde D, Sieper J, *et al*. Effects of long-term etanercept treatment on clinical outcomes and objective signs of inflammation in early nonradiographic axial spondyloarthritis: 104-week results from a randomized, placebo-controlled study. *Arthritis Care Res* 2017.
29 Dougados M, van der Heijde D, Sieper J, *et al*. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol* 2014;66:2091–102.
30 Maksymowych WP, Inman RD, Salonen D, *et al*. Spondyloarthritis research Consortium of Canada magnetic resonance imaging index for assessment of sacroiliac joint inflammation in ankylosing spondylitis. *Arthritis Rheum* 2005;53:703–9.
31 van den Berg R, Lenczner G, Thévenin F, *et al*. Classification of axial SpA based on positive imaging (radiographs and/or MRI of the sacroiliac joints) by local rheumatologists or radiologists versus central trained readers in the DESIR cohort. *Ann Rheum Dis* 2015;74:2016–21.
32 van den Berg R, de Hooge M, Bakker PA, *et al*. Metric Properties of the SPARCC Score of the Sacroiliac Joints - Data from Baseline, 3-month, and 12-month Followup in the SPACE Cohort. *J Rheumatol* 2015;42:1186–93.
33 Poddubnyy D, Sieper J. Similarities and differences between nonradiographic and radiographic axial spondyloarthritis: a clinical, epidemiological and therapeutic assessment. *Curr Opin Rheumatol* 2014;26:377–83.
34 Baraliakos X, Haibel H, Listing J, *et al*. Continuous long-term anti-TNF therapy does not lead to an increase in the rate of new bone formation over 8 years in patients with ankylosing spondylitis. *Ann Rheum Dis* 2014;73:710–5.
35 Haroon N, Inman RD, Learch TJ, *et al*. The impact of tumor necrosis factor α inhibitors on radiographic progression in ankylosing spondylitis. *Arthritis Rheum* 2013;65:2645–54.
36 Pedersen SJ, Wichuk S, Chiowchanwisawakit P, *et al*. Tumor necrosis factor inhibitor therapy but not standard therapy is associated with resolution of erosion in the sacroiliac joints of patients with axial spondyloarthritis. *Arthritis Res Ther* 2014;16:R100.

OPEN ACCESS

EXTENDED REPORT

Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study

Xavier Mariette,[1] Frauke Förger,[2] Bincy Abraham,[3] Ann D Flynn,[4] Anna Moltó,[5] René-Marc Flipo,[6] Astrid van Tubergen,[7] Laura Shaughnessy,[8] Jeff Simpson,[8] Marie Teil,[9] Eric Helmer,[10] Maggie Wang,[8] Eliza F Chakravarty[11]

Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-212196).

For numbered affiliations see end of article.

Correspondence to
Profesor Xavier Mariette, Université Paris-Sud, Hôpitaux Universitaires Paris-Sud, INSERM U1184, 63, rue Gabriel-Péri, 94270 Le Kremlin-Bicêtre, France; xavier.mariette@aphp.fr

Received 7 August 2017
Revised 22 September 2017
Accepted 1 October 2017
Published Online First 30 October 2017

ABSTRACT

Objectives There is a need for effective and safe treatment during pregnancy in women with chronic inflammatory diseases. This study evaluated placental transfer of certolizumab pegol (CZP), an Fc-free anti-tumour necrosis factor drug, from CZP-treated pregnant women to their infants.

Methods CRIB was a pharmacokinetic (PK) study of women ≥30 weeks pregnant receiving commercial CZP for a locally approved indication (last dose ≤35 days prior to delivery). Blood samples were collected from mothers, umbilical cords and infants at delivery, and infants again at weeks 4 and 8 post-delivery. CZP plasma concentrations were measured with a highly sensitive and CZP-specific electrochemiluminescence immunoassay (lower limit of quantification 0.032 µg/mL).

Results Sixteen women entered and completed the study. Maternal CZP plasma levels at delivery were within the expected therapeutic range (median [range] 24.4 [5.0–49.4] µg/mL). Of the 16 infants, 2 were excluded from the per-protocol set: 1 due to missing data at birth and 1 due to implausible PK data. Of the remaining 14 infants, 13 had no quantifiable CZP levels at birth (<0.032 µg/mL), and 1 had a minimal CZP level of 0.042 µg/mL (infant/mother plasma ratio 0.0009); no infants had quantifiable CZP levels at weeks 4 and 8. Of 16 umbilical cord samples, 1 was excluded due to missing data; 3/15 had quantifiable CZP levels (maximum 0.048 µg/mL).

Conclusions There was no to minimal placental transfer of CZP from mothers to infants, suggesting lack of *in utero* foetal exposure during the third trimester. These results support continuation of CZP treatment during pregnancy, when considered necessary.

Trial registration number NCT02019602; Results.

INTRODUCTION

Most chronic inflammatory diseases (CIDs) are more prevalent in women.[1] Disease onset tends to overlap with peak reproductive age, and women with CIDs are increasingly choosing to have children following diagnosis.[2] Adequate disease control is crucial to ensure the best foetal and maternal health, since high disease activity is associated with an increased risk of adverse pregnancy outcomes, including miscarriage, preterm delivery and low birth weight.[3–7] While disease activity may spontaneously improve during pregnancy, approximately 50% of women with rheumatic CIDs need effective therapeutic intervention and are faced with difficult questions regarding the impact of active disease on the foetus and the safety of different therapies during pregnancy.[8–12]

Anti-tumour necrosis factor (anti-TNF) drugs provide an effective therapeutic option that significantly improves the signs and symptoms of CIDs.[13] However, anti-TNF therapies are often discontinued after the first trimester to limit placental transfer of drug to the foetus.[14–16] Active transplacental transport of immunoglobulin G (IgG) from mother to infant is mediated by the neonatal fragment crystallisable (Fc) receptor (FcRn), a process that takes place mainly during the second and third trimesters of pregnancy.[15] Certolizumab pegol (CZP) is a PEGylated, Fc-free anti-TNF approved for the treatment of rheumatoid arthritis (RA), axial spondyloarthritis/ankylosing spondylitis (axSpA/AS), psoriatic arthritis (PsA), and Crohn's disease (CD). Because it lacks an IgG Fc region, unlike other anti-TNFs, CZP does not bind FcRn and is consequently not expected to undergo FcRn-mediated transfer across the placenta.[17] Preclinical data and findings from two investigator-initiated studies of pregnant women treated with anti-TNFs support the hypothesis that there is minimal placental transfer of CZP in humans.[18–21] However, the enzyme-linked immunosorbent assay (ELISA) used to measure CZP plasma levels in these studies was not specific for CZP, and it was not developed to measure the low CZP concentrations expected from placental transfer. Consequently, there is a need for more accurate and robust information to guide therapeutic decision making in women with CIDs regarding CZP treatment during pregnancy.

CRIB is the first industry-sponsored study designed to evaluate placental transfer of CZP from mothers to infants, by using a highly sensitive and specific assay to accurately measure the CZP plasma concentration in mothers, umbilical cords and infants at delivery, and in infants again at weeks 4 and 8 post-delivery.

METHODS

Study design and patients

CRIB (ClinicalTrials.gov, NCT02019602) was a prospective, postmarketing, multicentre, pharmacokinetic (PK) study designed to evaluate placental

To cite: Mariette X, Förger F, Abraham B, *et al*. *Ann Rheum Dis* 2018;**77**:228–233.

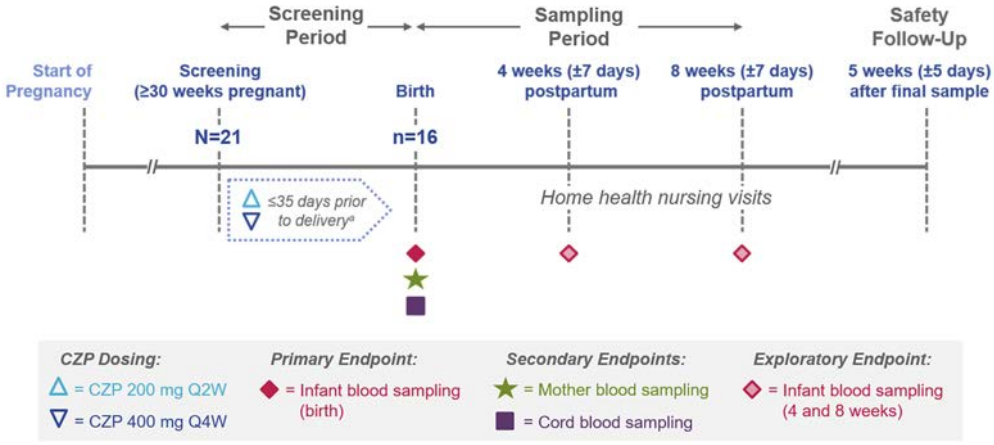


Figure 1 CRIB study design.
[a]Last certolizumab pegol (CZP) dose given within 35 days prior to delivery.

transfer of CZP from mothers to infants (figure 1). This study was conducted between January 2014 and November 2016 across 11 sites in France, Netherlands, Switzerland and the USA and was approved by local Institutional Review Boards. All women provided informed consent to participate and, together with the designated holder of parental rights, to enrol their infant in the study.

Eligible women were ≥30 weeks pregnant at the time of informed consent. Since CRIB was a postmarketing study, all women enrolled were being treated with commercial CZP for a locally approved indication (RA, axSpA/AS, PsA, and CD), as prescribed by their treating physicians. Patients were required to receive a CZP dose within 35 days prior to delivery. The decision to continue CZP treatment during pregnancy was made by the treating physicians prior to and independently from study participation. CZP was not provided by the study sponsor.

Patients with any pregnancy-related, clinically significant abnormality noted on obstetric ultrasound or other imaging assessment, with significant laboratory abnormalities during pregnancy, or with any evidence suggesting chronic or acute uteroplacental insufficiency were ineligible to participate. Mothers who had received treatment with any biologic or any anti-TNF other than CZP during pregnancy were excluded, as were mothers who were taking or had taken any medication with a strong risk of human foetal teratogenicity during pregnancy. Also excluded were mothers with a positive or indeterminate tuberculosis (TB) test at screening, with active or latent TB infection or at high risk for TB infection.

Study procedures

Mothers received commercial CZP on either the 2-weekly dose (CZP 200 mg every 2 weeks [Q2W]) or 4-weekly dose regimen (CZP 400 mg every 4 weeks [Q4W]), per their prescribers' discretion.

Maternal blood samples (≤4 mL per sample) were collected within 24 hours before or after delivery. Umbilical cord samples (≤4 mL per sample) were collected within 1 hour of birth. Infant blood samples (≤1.2 mL per sample) were collected within 24 hours after birth and at weeks 4 and 8 postpartum (figure 1). Samples collected at delivery/birth were obtained in the hospital setting, while in-home nursing visits at weeks 4 and 8 minimised the burden on mothers.

CZP concentration was measured in all plasma samples. Volume permitting, anti-CZP antibodies and total polyethylene glycol (PEG) levels (intact CZP, deconjugated PEG or other sources of PEG) were also measured. CZP and anti-CZP levels were measured at Covance Inc. (Chantilly, VA, USA). Total PEG levels were measured at Intertek Pharmaceutical Services (Manchester, UK).

CZP concentrations were measured using an electrochemiluminescence immunoassay validated in human plasma.[22] The assay was developed for optimal sensitivity and specificity: CZP was captured by a TNF-coated multiarray electrode and detected with an anti-PEG antibody, prior to reading on a MESO SCALE DISCOVERY platform (MSD; Rockville, MD, USA).[22] The assay is CZP-specific and >10 times more sensitive (lower limit of quantification [LLOQ] 0.032 μg/mL) than the previous ELISA used in other CZP PK studies.[20 23 24] Anti-CZP antibodies were measured using a previously validated ELISA (samples were positive if anti-CZP antibody levels were >2.4 units/mL).[24] Total PEG concentration was determined by nuclear magnetic resonance spectroscopy (LLOQ 2.5 μg/mL).

Study endpoints

The primary endpoint was the concentration of CZP in the infants' plasma at birth. CZP and anti-CZP antibody levels in the mothers' plasma and umbilical cords were secondary endpoints. Exploratory endpoints included CZP levels in the infants' plasma at weeks 4 and 8, anti-CZP antibody levels in the infants' plasma at birth and weeks 4 and 8, and PEG concentrations in the plasma of mothers, cords and infants.

Safety analyses included all mothers who received at least one dose of CZP, including screen failures, and infants of all mothers who entered the sampling period. Adverse events (AEs) were captured from the time of informed consent until the safety follow-up (5 weeks±5 days after final sample/withdrawal) and were coded using MedDRA V.18.1.

Statistical analysis

No formal sample size calculations were performed, as no statistical hypotheses were tested. The planned sample size was 20 mother–infant pairs. All PK variables were based on observed values; no imputation was used.

RESULTS

Patient disposition and baseline characteristics

A total of 21 CZP-treated pregnant women were screened. Five women discontinued screening, one due to serious AEs (SAEs) of placental insufficiency and premature baby, and four due

Table 1 Baseline characteristics of mothers and infants

Median (min, max), unless stated otherwise	Mothers (n=16)[a]
Age, years	31 (18, 40)
Mother's indication for CZP treatment, n	
Rheumatoid arthritis	11
Crohn's disease	3
Psoriatic arthritis	1
Axial spondyloarthritis/ankylosing spondylitis	1
Delivery type, n	
Vaginal	14
Caesarean section	2
Median (min, max), unless stated otherwise	**Infants (n=16)**
Female, n (%)	10 (62.5)
Gestational age at birth, weeks	39.9 (37.7, 41.7)
Weight at birth, kg	3.3 (2.6, 4.0)
Length at birth,[b] cm	49.5 (46.0, 55.9)
Head circumference at birth,[b] cm	34.5 (32.5, 37.0)
Normal APGAR score (7 to 10),[c] n	
At 1 min	16
At 5 min	16

[a]Mothers who entered the sampling period.
[b]n=15 (1 infant with missing data).
[c]APGAR scores range from 0 to 10; scores of 7 to 10 are considered normal.
APGAR, Appearance, Pulse, Grimace, Activity, Respiration; CZP, certolizumab pegol; max, maximum; min, minimum; Q2W, every 2 weeks; Q4W, every 4 weeks.

to ineligibility. Based on preliminary PK and safety analyses, which showed consistent data for the initial mother–infant pairs enrolled in the study, a final enrolment of 16 pregnant women was deemed sufficient to assess the primary objective.

All 16 mothers who entered the sampling period completed the study (no missed visits); 15 were on CZP 200 mg Q2W and one on CZP 400 mg Q4W. Median time between the last CZP dose and delivery was 11 days (range 1–27 days). Baseline characteristics of all participating mothers and their infants are shown in table 1. The gestational age and weight at birth of the 16 infants were within the expected range for healthy infants.

CZP plasma concentrations

Median CZP plasma level at delivery for all 16 participating mothers was 24.4 μg/mL (range 5.0–49.4 μg/mL). Of the 16 umbilical cord samples, one was excluded (sample not collected). Of the 15 remaining cord samples, only three had quantifiable CZP levels (0.035 μg/mL, 0.040 μg/mL, and 0.048 μg/mL); the maximum cord/mother plasma ratio for these three cords was 0.0025.

Of the 16 infants, two were excluded from the per-protocol set: one due to missing data at birth and one due to implausible PK data. The latter infant exhibited a high plasma CZP concentration at birth (0.485 μg/mL), while the week 4 and week 8 sample results were below the assay LLOQ (<0.032 μg/mL). Using two different PK modelling approaches, there was a very low probability (<0.1%) of an infant with this CZP concentration at birth to display levels below the LLOQ at week 4 (see online supplementary appendix for full investigation).

Of the 14 infants in the per-protocol set, 13 had no quantifiable CZP plasma levels at birth (<0.032 μg/mL), and one infant had a minimal CZP level at birth of 0.042 μg/mL (infant/mother plasma ratio 0.0009). No infants had quantifiable CZP plasma levels at week 4 (two samples missing) and week 8 (figure 2; online supplementary table 1). Nine mothers

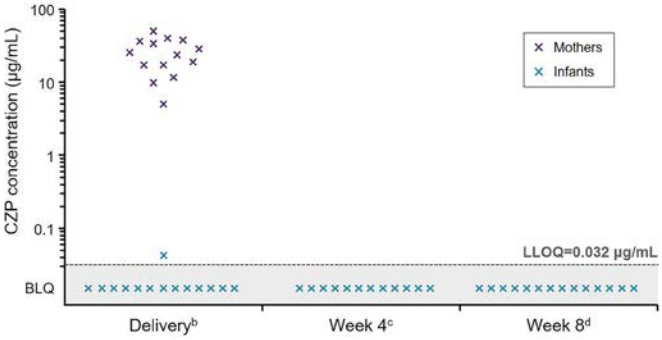


Figure 2 Plasma CZP concentrations in mothers and infants (n=14 mother–infant pairs[a]). [a]Two of 16 infants were excluded from the final per-protocol set: one due to missing data at birth and one due to implausible PK data (ie, data not consistent with a paediatric CZP PK model, based on the expected range of clearance, volume of distribution and subsequent elimination half-life; see online supplementary appendix); [b]Infant samples were collected within 24 hours post-delivery, while mother samples could be collected within 24 hours before or after delivery; [c]±7 days (two samples missing); [d]±7 days. BLQ, below the LLOQ (<0.032 μg/mL); CZP, certolizumab pegol; LLOQ, lower limit of quantification.

continued CZP postpartum and breastfed their infants; none of these infants had quantifiable CZP plasma levels.

PEG plasma concentrations

Median PEG plasma level at delivery for all 16 mothers was 30.0 μg/mL (range 10.1–59.9 μg/mL). Of 15 available umbilical cord samples, 14 had no quantifiable PEG; the remaining cord had 9.8 μg/mL PEG (corresponding CZP level was below LLOQ). Infant data were not interpretable, due to PEG contamination of the blood collection tubes (see online supplementary appendix).

Safety and immunogenicity analyses

Safety follow-up (up to 5 weeks±5 days after final sample/withdrawal) included the 21 CZP-exposed mothers screened and the 16 infants of all participating mothers. Overall, 15 mothers (71.4%) experienced 34 AEs, and 5 infants (31.3%) experienced 13 AEs; most AEs were mild to moderate (table 2). Two mothers reported severe AEs (arrested labour and prolonged labour), which were also classified as SAEs. All SAEs in the mothers were resolved, except for delivery of a premature baby. A severe AE of infection was reported in one infant, which was also an SAE (table 2). This infant had an unspecified infection indicated by elevated white blood cell count with no clinical signs. All infant SAEs were resolved. No congenital malformations were observed. No anti-CZP antibodies were detected in the mothers, umbilical cords or infants at any time point during the study.

DISCUSSION

Women diagnosed with CIDs during their reproductive years may need effective treatment to control disease activity during pregnancy.[1–7] However, the limited data published so far leave women and treating physicians in a difficult situation when deciding whether to continue anti-TNF therapy during pregnancy.[8–12 14–16] Although some recent treatment recommendations in rheumatology and gastroenterology state that CZP can be continued throughout pregnancy,[25–27] implementation in clinical practice varies greatly across the different specialities involved in the care of pregnant women. Disease flares during pregnancy are associated with an increased risk of miscarriage,

Table 2 Safety overview

n (%)[a]	Mothers (n=21)[b]	Infants (n=16)
Any TEAEs	15 (71.4)	5 (31.3)
Mild TEAEs	4 (19.0)	2 (12.5)
Moderate TEAEs	9 (42.9)	2 (12.5)
Severe TEAEs	2 (9.5)	1 (6.3)
Discontinuation due to TEAEs	2 (9.5)	0
Drug-related TEAEs	3 (14.3)	1 (6.3)
Serious TEAEs[c]	7 (33.3)	2 (12.5)
Deaths	0	0
Serious TEAEs by mother–infant pair		
SF	Placental insufficiency Premature baby	N/A
1	Arrested labour	None
2	**Arrested labour**	None
3	**Prolonged labour**	None
4	Gestational diabetes Polyhydramnios	None
5	None	Hypoglycaemia **Infection**
6	Perineal abscess	None
7	Vaginal laceration	Macrosomia Meconium in amniotic fluid

TEAEs were defined as any adverse event (AE) captured from the time of informed consent until the safety follow-up; bold text indicates severe TEAEs.
[a]Number of mothers or infants reporting at least one AE for the indicated category.
[b]Safety set for mothers (includes five screen failures).
[c]Serious TEAEs were classified using the United States Food and Drug Administration regulatory definition of serious AEs.
TEAE, treatment-emergent adverse event; SF, screen failure; N/A, not applicable.

preterm delivery and low birth weight,[3–7] and may be more deleterious to neonatal outcomes than any potential risks associated with anti-TNF therapy.[14 16] Therefore, disease activity should be controlled through optimised medical therapy throughout pregnancy, taking into consideration the possible influence of anti-TNFs on the immune response of the *in utero* exposed infant.

CRIB was the first industry-sponsored PK study evaluating placental transfer of a biologic, CZP, from mothers to their infants. Maternal CZP plasma concentrations were within the expected therapeutic range,[23 24] confirming that all mothers in the CRIB study were adequately exposed to CZP at the time of delivery. Using the new, highly sensitive and CZP-specific assay, 13 of 14 infants had no quantifiable CZP plasma levels at birth. In the single infant with a measurable level at birth, the CZP concentration was 0.09% of the maternal CZP plasma level, which is unlikely to have any clinical relevance. At weeks 4 and 8 postpartum, there were no quantifiable CZP levels in the infants' plasma. Umbilical cord data were in agreement with the infant plasma results. AEs in the mothers were consistent with the known safety profile of CZP, and events expected during pregnancy in unexposed women with these underlying CIDs. AEs experienced by the infants did not show any patterns or clusters of events suggesting a specific safety signal in children.[28]

To date, two investigator-initiated studies on placental transfer of anti-TNFs have been published: one in women with CD by Mahadevan *et al*. (maternal, cord and infant samples collected at birth)[20] and one in women with RA and axSpA by Förger *et al*. (maternal and cord samples collected at birth).[19] CRIB greatly expands on the available data, because it was designed to evaluate placental transfer of CZP and to further understand the PK profile of CZP at 4 and 8 weeks in the *in utero* exposed infant, in the event of placental transfer. Furthermore, to enhance the accuracy of CZP measurement, a new electrochemiluminescence assay was developed.[22] This technology offered significantly improved specificity and sensitivity over the ELISA previously used by Mahadevan *et al*. and Förger *et al*.[20 23 24]

ELISAs provide a relatively simple, high-throughput method of measuring drug concentrations in human blood. Using this type of assay, Mahadevan *et al*. showed low levels of placental transfer of CZP (median cord/mother percentage 3.9%), compared to adalimumab (median cord/mother percentage 153%) and infliximab (median cord/mother percentage 160%).[20] Förger *et al*. reported similar findings for CZP (maximum cord/mother percentage 3.8%).[19] Although the ELISA used in these two studies conforms to regulatory guidelines and has been validated to measure the therapeutic range of CZP concentrations typically seen in treated adults, it was not developed to measure the low CZP concentrations expected from placental transfer (LLOQ of the ELISA 0.41 μg/mL). Furthermore, the detection reagent used was an anti-human kappa light chain antibody, which is not specific for CZP and can detect other TNF-binding antibodies, such as other therapeutic anti-TNF antibodies, or naturally occurring autoantibodies to TNFα, which can be found both in patients with CIDs and otherwise healthy individuals.[29] By contrast, the new electrochemiluminescence assay used in CRIB is highly specific for CZP, since it uses a TNF-coated electrode to capture CZP and an anti-PEG antibody as the detection reagent. In addition, at an LLOQ of 0.032 μg/mL, the new assay is over 10 times more sensitive than the previous ELISA.[22] Consequently, this assay enabled us to provide much more accurate data regarding placental transfer of CZP, which can be translated with greater confidence into evidence-based clinical practice.

One limitation of the CRIB study is the fact that the PK profile of CZP in pregnant women was not fully characterised during pregnancy, since maternal samples were collected only at delivery. It would be valuable to measure maternal CZP concentrations earlier in pregnancy and to investigate the potential impact of the loading dose (CZP 400 mg at weeks 0, 2 and 4) in women initiating CZP treatment while pregnant. Further research is needed to answer these questions.

It has been suggested that TNFα may play a role in the normal development of the immune system.[30] However, TNFα-deficient mice generated by gene targeting have normal secondary lymphoid organs, suggesting that TNFα is not necessary for lymphoid organogenesis.[31] Surprisingly, these mice lack primary B cell follicles in the spleen, although this functional defect can be rescued by complementation of TNFα expression.[31 32] While rodents develop B cell follicles and germinal centres early in pregnancy, in humans, this process starts in the third trimester and continues through week 8 postpartum.[33] The results of the CRIB study suggest no to minimal placental transfer of CZP during the third trimester, and the minimal level detected in one infant at birth (<0.1% of the adult therapeutic level) can be assumed to have no effect on immune system development. Furthermore, a study in pregnant macaque monkeys examined the effect of the anti-TNF golimumab during organogenesis and the perinatal/postnatal period. Golimumab, which has an Fc portion and is therefore expected to actively cross the placenta, was found at high concentrations in neonatal macaques and persisted for 6 months postpartum. However, there were no significant repercussions on lymphoid organ development and immune function, suggesting once again that TNFα may be dispensable for the immune system development during pregnancy.[34]

Humans are born with an immature immune system and have an increased risk of infection compared to adults, relying on innate immune responses and maternal antibodies transferred across the placenta and via breast milk.[30] So far, few studies have examined the long-term safety of anti-TNFs in antenatally exposed children.[35 36] With the exception of CZP, all approved anti-TNFs (infliximab, adalimumab, golimumab and etanercept) contain an IgG1 Fc region, which enables FcRn-mediated transport across the placenta.[20 30] In a prospective study of infants born to mothers who received anti-TNFs during pregnancy, adalimumab and infliximab could be detected in infant blood until 12 months of age, due to IgG recycling in neonates via FcRn.[35] This has raised concerns regarding the potential risk of infection and the challenges of vaccinating infants exposed to anti-TNFs *in utero*. By contrast, in CRIB, there were no quantifiable CZP levels in the infants' plasma at weeks 4 and 8 after birth, and AEs experienced by the infants did not suggest a specific safety signal. While these results can be considered reassuring, long-term observational studies are needed to fully characterise the safety profile of CZP in the infants of exposed mothers.

In addition to the influence of anti-TNFs on the neonatal immune system, it is also important to take into account the potential impact of intrauterine exposure earlier in pregnancy, particularly during the first trimester, before the placenta is fully formed and when organogenesis takes place. Recent systematic reviews and meta-analyses have found no association of anti-TNF exposure during the first trimester with adverse pregnancy outcomes.[25 37 38] Furthermore, evidence gathered through pharmacovigilance reporting supports the conclusion that maternal CZP exposure during the first trimester does not appear to increase the risk of adverse neonatal outcomes or major congenital malformations.[39] Of note, 10 of the 14 infants in CRIB were born to mothers exposed during the first trimester.

In conclusion, our data indicate no to minimal placental transfer of CZP from mothers to infants, suggesting a lack of *in utero* foetal exposure during the third trimester. Combined with the evidence currently available regarding pregnancy outcomes in women exposed to CZP during the first trimester, which indicate no increased rate of major congenital malformations,[39] the results of the CRIB study support the continuation of CZP treatment throughout pregnancy when considered necessary to control disease activity.

Author affiliations
[1]Université Paris-Sud, Hôpitaux Universitaires Paris-Sud, INSERM, Le Kremlin-Bicêtre, France
[2]Inselspital, University Hospital and University of Bern, Bern, Switzerland
[3]Houston Methodist Hospital, Houston, Texas, USA
[4]University of Utah Health, Salt Lake City, Utah, USA
[5]Department of Rheumatology, Hôpital Cochin, Assistance Publique – Hôpitaux de Paris, INSERM, Paris, France
[6]Centre Hospitalier Regional Universitaire de Lille, Lille, Nord-Pas-de-Calais, France
[7]Department of Medicine, Division of Rheumatology and CAPHRI - Care and Public Health Research Institute Maastricht, Maastricht University Medical Center, Maastricht, Netherlands
[8]UCB Pharma, Raleigh, North Carolina, USA
[9]UCB Pharma, Slough, UK
[10]UCB Pharma, Brussels, Belgium
[11]Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, USA

Acknowledgements This study was funded by UCB Pharma. We are indebted to the mothers and their infants for their altruistic participation in this study. We thank the nurses and the investigator teams, the study coordination team including Samia Elyakhlifi and Lien Heinzen, UCB Pharma, and Nicole Hurst, PPD. We also acknowledge Amanda Golembesky, UCB Pharma, Raleigh, NC, USA, and Gerry Parker, UCB Pharma, Slough, UK, for their contributions; Cécile Ecoffet, PharmD, and Simone E. Auteri, MSc, UCB Pharma, Brussels, Belgium, for publication coordination; and Ricardo Milho, PhD, and Julia Bárdos, PhD, from Costello Medical, Cambridge, UK, for medical writing and editorial assistance in preparing this manuscript for publication, based on the authors' input and direction.

Contributors XM, FF, BA, ADF, AM, R-MF, AvT, LS, JS, MT, EH, MW and EC contributed to the conception, design, execution or analysis and interpretation of the data. All authors approved the final version of the manuscript for publication.

Funding UCB Pharma sponsored the study and the development of the manuscript and reviewed the text to ensure that from a UCB Pharma perspective, the data presented in the publication are scientifically, technically and medically supportable, that they do not contain any information that has the potential to damage the intellectual property of UCB Pharma and that the publication complies with applicable laws, regulations, guidelines and good industry practice. The authors approved the final version to be published after critically revising the manuscript for important intellectual content.

Competing interests XM: grant/research support: Biogen, Pfizer, UCB Pharma; consultant for BMS, GSK, LFB, Pfizer, UCB Pharma. FF: grant/research support: UCB Pharma; speaker's fees: Mepha, Roche, UCB Pharma. BA: grant/research support: Janssen-Cilag, UCB Pharma; speaker's fees: AbbVie, American Reagent, Janssen-Cilag, UCB Pharma. AF: grant/research support: UCB Pharma. AM: grant/research support: MSD, AbbVie, Pfizer and UCB Pharma; consultant for: MSD, AbbVie, Pfizer, UCB Pharma. R-MF: grant/research support and consultant for: UCB Pharma. AvT: grant/research support: Pfizer, AbbVie, UCB Pharma, Janssen-Cilag, Celgene, Novartis; speaker's fees: MSD, Janssen-Cilag, Pfizer; consultant for: AbbVie, Novartis, Janssen-Cilag, Pfizer. LS: employee of UCB Pharma. JS: employee of UCB Pharma. MT: employee of UCB Pharma. EH: employee of UCB Pharma. MW: employee of UCB Pharma. EC: grant/research support: UCB Pharma.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval This study was conducted between January 2014 and November 2016 across 11 sites in France, Netherlands, Switzerland and the USA and was approved by local Institutional Review Boards.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Kavanaugh A, Cush JJ, Ahmed MS, *et al*. Proceedings from the American College of Rheumatology Reproductive Health Summit: the management of fertility, pregnancy, and lactation in women with autoimmune and systemic inflammatory diseases. *Arthritis Care Res* 2015;67:313–25.
2 Chakravarty E, Clowse ME, Pushparajah DS, *et al*. Family planning and pregnancy issues for women with systemic inflammatory diseases: patient and physician perspectives. *BMJ Open* 2014;4:e004081.
3 Bröms G, Granath F, Linder M, *et al*. Birth outcomes in women with inflammatory bowel disease: effects of disease activity and drug exposure. *Inflamm Bowel Dis* 2014;20:1091–8.
4 de Man YA, Hazes JM, van der Heide H, *et al*. Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. *Arthritis Rheum* 2009;60:3196–206.
5 Jakobsson GL, Stephansson O, Askling J, *et al*. Pregnancy outcomes in patients with ankylosing spondylitis: a nationwide register study. *Ann Rheum Dis* 2016;75:1838–42.
6 Mahadevan U, Sandborn WJ, Li DK, *et al*. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. *Gastroenterology* 2007;133:1106–12.
7 Nørgaard M, Larsson H, Pedersen L, *et al*. Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study. *J Intern Med* 2010;268:329–37.
8 Mouyis MA, Thornton CC, Williams D, *et al*. Pregnancy outcomes in patients with psoriatic arthritis. *J Rheumatol* 2017;44:128–9.
9 Jethwa H, Lam S, Giles I. O26 Does inflammatory arthritis really improve during pregnancy? A systematic review and meta-analysis. *Rheumatology* 2014;53(suppl 1):i40.
10 Polachek A, Li S, Polachek IS, *et al*. Psoriatic arthritis disease activity during pregnancy and the first-year postpartum. *Semin Arthritis Rheum* 2017;46:740–5.

11 de Man YA, Dolhain RJ, van de Geijn FE, *et al*. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum* 2008;59:1241–8.
12 Pedersen N, Bortoli A, Duricova D, *et al*. The course of inflammatory bowel disease during pregnancy and postpartum: a prospective European ECCO-EpiCom Study of 209 pregnant women. *Aliment Pharmacol Ther* 2013;38:501–12.
13 Tracey D, Klareskog L, Sasso EH, *et al*. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther* 2008;117:244–79.
14 Gisbert JP, Chaparro M. Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease. *Am J Gastroenterol* 2013;108:1426–38.
15 Hazes JM, Coulie PG, Geenen V, *et al*. Rheumatoid arthritis and pregnancy: evolution of disease activity and pathophysiological considerations for drug use. *Rheumatology* 2011;50:1955–68.
16 Hyrich KL, Verstappen SM. Biologic therapies and pregnancy: the story so far. *Rheumatology* 2014;53:1377–85.
17 Baker T, Kevorkian L, Nesbitt A. FRI0162 Investigation into the binding affinity of certolizumab pegol to FcRn and functional consequences for FcRn-mediated transcytosis: comparison to infliximab, adalimumab and etanercept. *Ann Rheum Dis* 2013;72(Suppl 3):A426.1–A426.
18 Brown D, Nesbitt A, Stephens S, *et al*. Lack of placental transfer and accumulation in milk of an anti-TNF PEGylated Fab' fragment in rats: P-0030. *Inflammatory bowel diseases* 2007;13:656.
19 Förger F, Zbinden A, Villiger PM. Certolizumab treatment during late pregnancy in patients with rheumatic diseases: low drug levels in cord blood but possible risk for maternal infections. A case series of 13 patients. *Joint Bone Spine* 2016;83:341–3.
20 Mahadevan U, Wolf DC, Dubinsky M, *et al*. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013;11:286–92.
21 Porter C, Armstrong-Fisher S, Kopotsha T, *et al*. Certolizumab pegol does not bind the neonatal Fc receptor (FcRn): consequences for FcRn-mediated in vitro transcytosis and ex vivo human placental transfer. *J Reprod Immunol* 2016;116:7–12.
22 Smeraglia J, Silva JP, Jones K. Improving the sensitivity and specificity of a bioanalytical assay for the measurement of certolizumab pegol. *Bioanalysis* 2017;9:1217–26.
23 Lacroix BD, Parker GL. S1029 Dosing with certolizumab pegol (CZP) 200 mg every 2 weeks (Q2W) provides higher plasma trough concentrations than 400 mg every 4 weeks (Q4W). *Gastroenterology* 2010;138:S-163–4.
24 Wade JR, Parker G, Kosutic G, *et al*. Population pharmacokinetic analysis of certolizumab pegol in patients with Crohn's disease. *J Clin Pharmacol* 2015;55:866–74.
25 Götestam Skorpen C, Hoeltzenbein M, Tincani A, *et al*. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis* 2016;75:795–810.
26 Mahadevan U, Cucchiara S, Hyams JS, *et al*. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: pregnancy and pediatrics. *Am J Gastroenterol* 2011;106:214–23.
27 Flint J, Panchal S, Hurrell A, *et al*. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology* 2016;55:1693–7.
28 Kliegman R, Stanton B, Saint Geme J, *et al*. *Nelson Textbook of Pediatrics*. 20th ed: Elsevier Health Sciences, 2015.
29 Fomsgaard A, Svenson M, Bendtzen K. Auto-antibodies to tumour necrosis factor alpha in healthy humans and patients with inflammatory diseases and gram-negative bacterial infections. *Scand J Immunol* 1989;30:219–23.
30 Arsenescu R, Arsenescu V, de Villiers WJ. TNF-α and the development of the neonatal immune system: implications for inhibitor use in pregnancy. *Am J Gastroenterol* 2011;106:559–62.
31 Pasparakis M, Alexopoulou L, Episkopou V, *et al*. Immune and inflammatory responses in TNF alpha-deficient mice: a critical requirement for TNF alpha in the formation of primary B cell follicles, follicular dendritic cell networks and germinal centers, and in the maturation of the humoral immune response. *J Exp Med* 1996;184:1397–411.
32 Wen L, Shinton SA, Hardy RR, *et al*. Association of B-1 B cells with follicular dendritic cells in spleen. *J Immunol* 2005;174:6918–26.
33 Holsapple MP, West LJ, Landreth KS. Species comparison of anatomical and functional immune system development. *Birth Defects Res B Dev Reprod Toxicol* 2003;68:321–34.
34 Martin PL, Oneda S, Treacy G. Effects of an anti-TNF-alpha monoclonal antibody, administered throughout pregnancy and lactation, on the development of the macaque immune system. *Am J Reprod Immunol* 2007;58:138–49.
35 Julsgaard M, Christensen LA, Gibson PR, *et al*. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. *Gastroenterology* 2016;151:110–9.
36 Mahadevan U, Martin C, Kane SV, *et al*. 437 Do infant serum levels of biologic agents at birth correlate with risk of adverse outcomes? Results from the PIANO registry. *Gastroenterology* 2016;150:S91–S92.
37 Komaki F, Komaki Y, Micic D, *et al*. Outcome of pregnancy and neonatal complications with anti-tumor necrosis factor-α use in females with immune mediated diseases; a systematic review and meta-analysis. *J Autoimmun* 2017;76:38–52.
38 Mozaffari S, Abdolghaffari AH, Nikfar S, *et al*. Pregnancy outcomes in women with inflammatory bowel disease following exposure to thiopurines and antitumor necrosis factor drugs: a systematic review with meta-analysis. *Hum Exp Toxicol* 2015;34:445–59.
39 Clowse MEB, Scheuerle AE, Chambers CD, *et al*. Characteristics and outcomes of prospectively reported pregnancies exposed to certolizumab pegol from a safety database. *Arthritis Rheumatol* 2017;69(Suppl 10(). [abstract 1309].

OPEN ACCESS

EXTENDED REPORT

Safety, immunogenicity and efficacy after switching from reference infliximab to biosimilar SB2 compared with continuing reference infliximab and SB2 in patients with rheumatoid arthritis: results of a randomised, double-blind, phase III transition study

Josef S Smolen,[1] Jung-Yoon Choe,[2] Nenad Prodanovic,[3] Jaroslaw Niebrzydowski,[4] Ivan Staykov,[5] Eva Dokoupilova,[6,7] Asta Baranauskaite,[8] Roman Yatsyshyn,[9] Mevludin Mekic,[10] Wieslawa Porawska,[11] Hana Ciferska,[12] Krystyna Jedrychowicz-Rosiak,[13] Agnieszka Zielinska,[14] Younju Lee,[15] Young Hee Rho[15]

Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-211741).

For numbered affiliations see end of article.

Correspondence to
Professor Josef S Smolen, Division of Rheumatology Department of Medicine 3 Medical University of Vienna Waehringer Guertel 18-20 Vienna A-1090, Austria; josef.smolen.ard@meduniwien.ac.at

A portion of this manuscript, including results up to week 78, has been previously presented at EULAR 2016 (Poster # FRI0162) and published in abstract form as follows: Smolen JS, Choe J-Y, Prodanovic N, et al. Comparable safety and immunogenicity and sustained efficacy after transition to SB2 (an infliximab biosimilar) vs ongoing infliximab reference product in patients with rheumatoid arthritis: results of phase III transition study. Ann Rheum Dis 2016;75(Suppl 2):488.

Received 5 May 2017
Revised 22 September 2017
Accepted 4 October 2017
Published Online First 17 October 2017

To cite: Smolen JS, Choe J-Y, Prodanovic N, *et al*. *Ann Rheum Dis* 2018;**77**:234–240.

ABSTRACT

Objectives Efficacy, safety and immunogenicity results from the phase III study of SB2, a biosimilar of reference infliximab (INF), were previously reported through 54 weeks. This transition period compared results in patients with rheumatoid arthritis (RA) who switched from INF to SB2 with those in patients who maintained treatment with INF or SB2.

Methods Patients with moderate to severe RA despite methotrexate treatment were randomised (1:1) to receive SB2 or INF at weeks 0, 2 and 6 and every 8 weeks thereafter until week 46. At week 54, patients previously receiving INF were rerandomised (1:1) to switch to SB2 (INF/SB2 (n=94)) or to continue on INF (INF/INF (n=101)) up to week 70. Patients previously receiving SB2 continued on SB2 (SB2/SB2 (n=201)) up to week 70. Efficacy, safety and immunogenicity were assessed up to week 78.

Results Efficacy was sustained and comparable across treatment groups. American College of Rheumatology (ACR) 20 responses between weeks 54 and 78 ranged from 63.5% to 72.3% with INF/SB2, 66.3%%–69.4% with INF/INF and 65.6%–68.3% with SB2/SB2. Treatment-emergent adverse events during this time occurred in 36.2%, 35.6% and 40.3%, respectively, and infusion-related reactions in 3.2%, 2.0% and 3.5%. Among patients who were negative for antidrug antibodies (ADA) up to week 54, newly developed ADAs were reported in 14.6%, 14.9% and 14.1% of the INF/SB2, INF/INF and SB2/SB2 groups, respectively.

Conclusions The efficacy, safety and immunogenicity profiles remained comparable among the INF/SB2, INF/INF and SB2/SB2 groups up to week 78, with no treatment-emergent issues or clinically relevant immunogenicity after switching from INF to SB2.

Trial registration number NCT01936181; EudraCT number: 2012-005733-37.

INTRODUCTION

The introduction of biosimilars has significantly impacted medical practice and the pharmaceutical industry.[1 2] While biologicals are effective, they are also expensive, thus creating inequity by limiting their accessibility to patients and countries that can afford them.[3 4] Biosimilars have the potential to improve access to treatment by reducing the financial burden on healthcare systems.[5]

While from a physician's perspective, biosimilars may be considered akin to chemical generics, making identical copies of biologicals is not technically feasible, and biosimilars undergo a more comprehensive regulatory pathway. This includes preclinical quality analysis, pharmacokinetic and pharmacodynamic assessments and phase III clinical evaluation, which is usually conducted in a randomised, double-blind fashion in at least one of the originator's indications.[6 7] Clinical trials of biosimilars are usually parallel-arm equivalence studies, with the primary aim to test that the biosimilar has equivalent efficacy and comparable safety to the reference product.[6–10]

An important issue surrounding biosimilars that cannot be tested by this approach is whether patients can be switched from the originator without major concerns.[1] Because the main objective of biosimilars is to reduce drug costs and make biologicals more affordable to a larger population,[11] switching patients from the original biological to a biosimilar is a likely consideration in clinical practice to capitalise on the cost reduction. However, as previously mentioned, biosimilars are not identical to their original counterparts. Additionally, biologicals commonly have issues with immunogenicity, which can be associated with decreased efficacy and, in some cases, with adverse events (AEs).[12] Therefore, data regarding switching from originators to biosimilars are desirable to strengthen the demonstration of biosimilarity.

SB2 (Samsung Bioepis, Incheon, Republic of Korea) and reference infliximab (INF; Remicade, Janssen Biotech, Horsham, Pennsylvania, USA) have been shown to have equivalent efficacy and comparable structure, function, pharmacokinetic parameters, immunogenicity and safety.[8 13 14] SB2 was approved in the USA on 21 April 2017 and has also been approved in Norway, Liechtenstein, Iceland and Australia, in addition to having been approved in the European Union[15] and Korea.[16]

The clinical efficacy and safety results of SB2 for the treatment of rheumatoid arthritis (RA) were previously reported, up to 54 weeks, based on a phase III equivalence study conducted using the aforementioned parallel-arm design.[8 17] The objectives of the present transition-extension period (described as transition period hereafter) of the phase III study were to investigate whether individuals on INF could be readily switched to SB2 without major concerns and whether comparable efficacy, safety and immunogenicity were maintained after the switch when compared with both ongoing reference INF as well as SB2.

METHODS

Methods for the initial randomised, double-blind period of this multinational, multicentre, parallel group study (weeks 0–54) have been previously described.[8 17] The study originally enrolled patients 18–75 years of age diagnosed with moderate to severe RA (1987 American College of Rheumatology (ACR) criteria) despite methotrexate therapy. The methods below focus on the transition period (weeks 54–78).

Patients

Those who completed the week 54 visit of the randomised, double-blind period and were willing to participate were eligible for the transition period. Patients who experienced any significant medical condition(s) during the randomised, double-blind period, such as the occurrence of a serious AE (SAE) or intolerance of SB2 or INF, and who were determined to be unfit for further treatment were excluded.

Study design

Patients were initially randomised (1:1) to receive either SB2 or INF at weeks 0, 2 and 6 and then every 8 weeks thereafter until week 46 (randomised, double-blind period). The protocol was amended during this period to accommodate the transition design. At week 54, enrolled patients in the INF group were rerandomised (1:1) to either transition (switch) to SB2 (INF/SB2) or to continue on INF (INF/INF) up to week 70 (transition period, figure S1 in online supplementary appendix). Patients in the SB2 group continued to receive SB2 up to week 70 (SB2/SB2) but followed the randomisation procedure to maintain double-blind status. The final visit was at week 78. An interactive web response system was used for randomisation and treatment allocation.[8]

Treatment with SB2 or INF was initiated at an intravenous dose of 3 mg/kg at week 0. The dose could have been increased stepwise by 1.5 mg/kg, up to a maximum of 7.5 mg/kg, starting at week 30 and every 8 weeks thereafter if the patient's RA symptoms were not well controlled by the existing dose. At the time of switching to SB2 from INF (or continuing INF or SB2 in the other arms), the dosing schedule continued from the last dose applied before switching (ie, week 54). An oral or parenteral stable dose of methotrexate (10–25 mg/week) was taken with folic acid (5–10 mg/week) throughout the study. No other disease-modifying antirheumatic drugs were permitted. Paracetamol, antihistamines and/or corticosteroids were allowed as premedications at the investigator's discretion to prevent infusion-related reactions.

Assessments

At each clinic visit, efficacy was evaluated by ACR response rates (ACR20, ACR50 and ACR70), disease activity score based on a 28-joint count (DAS28 score) and European League Against Rheumatism (EULAR) responses. Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) scores[18] were calculated post hoc. Safety was monitored throughout the study by evaluation of treatment-emergent AEs (TEAEs), SAEs and AEs of special interest (serious infections or tuberculosis); latent tuberculosis was monitored with QuantiFERON Gold

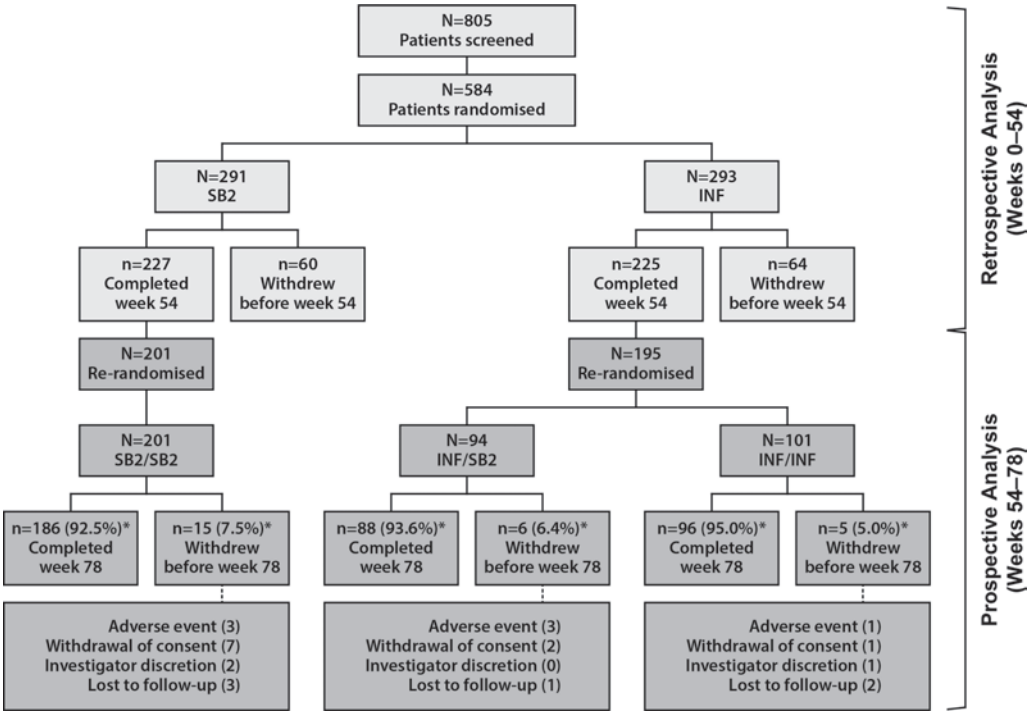


Figure 1 Patient disposition of the study population. *Percentages of patients completed and discontinued are based on the number of patients rerandomised at week 54. Note: eight patients' data from sites in eastern Ukraine were excluded from the analysis because of regional issues (n=4 in SB2, n=4 in INF). INF, reference infliximab.

Table 1 Patient demographics and disease characteristics of the rerandomised population at baseline (A and B) and rerandomisation (C)

Variable	INF/SB2 (n=94)	INF/INF (n=101)	SB2/SB2 (n=201)
A. Demographics at baseline (week 0)			
Age, years	53.0±11.0	51.5±11.2	51.8±12.1
Female, n (%)	77 (81.9)	79 (78.2)	158 (78.6)
Race white, n (%)	87 (92.6)	88 (87.1)	183 (91.0)
Height, cm	165.7±8.0	165.4±7.5	165.2±9.0
Weight, kg	72.2±14.9	73.1±17.4	72.7±14.7
BMI, kg/m^2	26.3±5.1	26.8±6.4	26.6±5.0
Disease duration, years	6.3±5.4	6.7±6.1	6.3±6.2
Rheumatoid factor positive, n (%)	67 (71.3)	66 (65.3)	140 (69.7)
B. Disease characteristics at baseline (week 0)			
Tender joint count (0–68)	23.7±11.3	24.6±11.6	23.9±12.2
Swollen joint count (0–66)	14.6±7.6	14.3±7.2	14.1±6.8
Duration of MTX use, months	49.7±45.4	52.1±50.6	51.1±46.8
MTX dose at baseline, mg/week	14.3±3.9	15.2±4.0	14.7±4.1
C reactive protein, mg/L	13.8±21.9	13.7±18.8	12.0±19.1
ESR, mm/hour	45.7±23.0	45.3±19.7	43.0±17.5
HAQ-DI (0–3)	1.5±0.6	1.5±0.5	1.5±0.6
Patient pain VAS (0–100), mm	60.9±20.4	66.7±19.0	60.0±17.9
Patient VAS (0–100), mm	62.8±18.1	64.3±17.4	61.7±17.3
Physician VAS (0–100), mm	61.9±16.2	62.0±14.5	60.8±15.1
DAS28 (ESR)	6.5±0.7	6.6±0.8	6.4±0.8
SDAI	40.2±11.6	40.2±11.0	38.9±11.0
CDAI	38.8±11.3	38.9±10.6	37.7±10.7
C. Disease characteristics at rerandomisation (week 54)			
Tender joint count (0–68)	6.2±7.0	8.2±10.5	7.3±9.2
Swollen joint count (0–66)	2.7±4.4	4.0±6.1	3.4±5.2
C reactive protein, mg/L	6.6±12.4	8.2±12.7	8.4±12.6
ESR, mm/hour	27.7±21.9	28.3±19.6	28.3±20.0
HAQ-DI (0–3)	1.0±0.6	1.0±0.6	1.0±0.7
Patient pain VAS (0–100), mm	35.9±23.4	35.8±22.7	35.6±23.8
Patient VAS (0–100), mm	35.5±22.6	35.8±21.9	34.8±23.3
Physician VAS (0–100), mm	24.5±18.1	25.0±17.1	25.1±18.0
DAS28 (ESR)	3.9±1.3	4.1±1.5	4.0±1.4
SDAI	13.2±10.0	15.2±12.0	14.6±12.2
CDAI	12.5±9.8	14.3±11.7	13.8±11.8
Infliximab dose, mg/kg	3.78±1.16	3.91±1.38	3.85±1.25

Values represent mean±SD or number (percentage) of patients.
BMI, body mass index; CDAI, Clinical Disease Activity Index; DAS28, disease activity score based on a 28-joint count; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire of Disability Index; INF, reference infliximab; MTX, methotrexate; SDAI, simplified disease activity index; VAS, visual analogue scale.

blood tests at weeks 54 and 78. Immunogenicity was assessed by the development of serum antidrug antibodies (ADAs) and neutralising antibodies (NAb) among who were ADA positive.[8]

Statistical analysis

Sample size and power calculations based on the primary endpoint of the study (ACR20 response at week 30) were previously described.[8] All results obtained during the transition period were analysed using descriptive statistics. Efficacy results were based on the extended full analysis set (Ex-FAS), which follows the intent-to-treat principle and comprises available data (ie, no imputation) in all patients who were rerandomised at week 54 and who received at least one dose of SB2 or INF during the transition period. To evaluate efficacy changes over the entire duration of the study in the three treatment groups, a retrospective analysis of efficacy was performed in the Ex-FAS population from week 54 back to week 0. AEs and immunogenicity were analysed in the extended safety set (Ex-SAF), which comprised all patients who received at least one dose of SB2 or INF during the transition period. Analyses were performed using SAS V.9.2.

RESULTS

Patients

The study started in August 2013, and the transition period was completed in August 2015. Patient disposition is shown in figure 1. At week 54, 396 patients were rerandomised to receive SB2/SB2 (n=201), INF/SB2 (n=94) or INF/INF (n=101) and were included in this analysis. The majority of patients in each treatment group completed the transition period (92.5%, 93.6% and 95.0%, respectively). The number and pattern of withdrawals were comparable among the three treatment groups.

Patient demographics and disease characteristics of the rerandomised population were well balanced among the three treatment groups at baseline, and disease characteristics were also comparable at the time of rerandomisation (table 1). At weeks

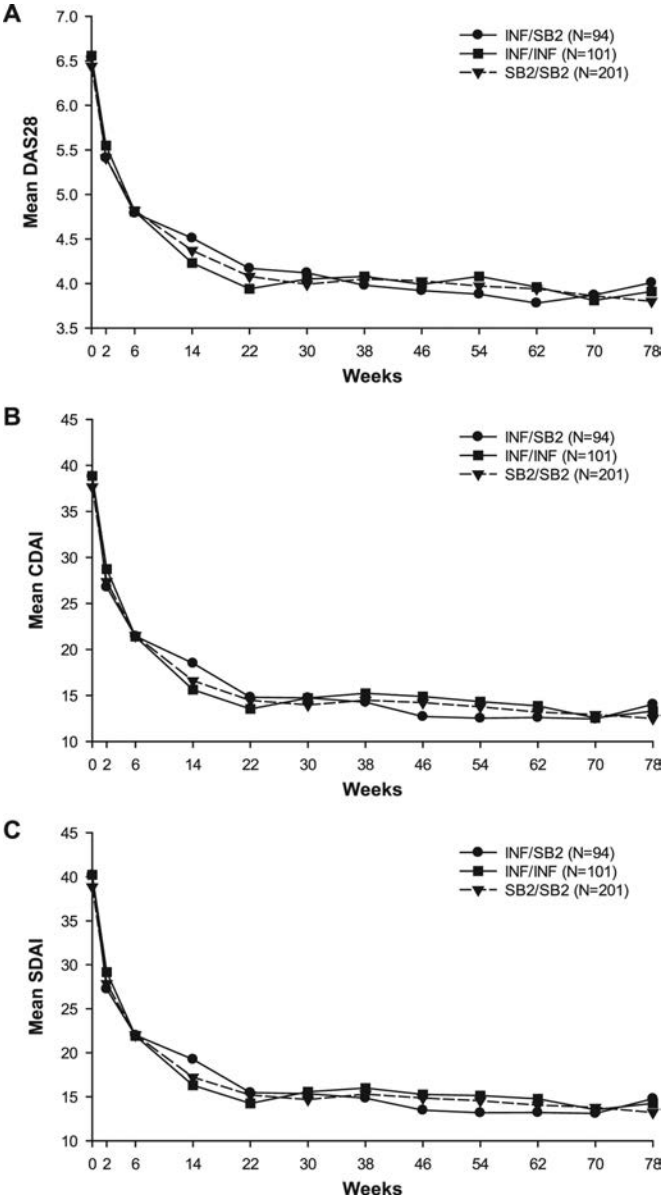


Figure 2 Mean disease activity score based on a 28-joint count (DAS28 (ESR)) (A), Clinical Disease Activity Index (CDAI) score (B) and Simplified Disease Activity Index (SDAI) score (C) up to week 78. ESR, erythrocyte sedimentation rate; INF, reference infliximab.

54, 62 and 70, the proportion of patients treated with 3, 4.5, 6 or 7.5 mg/kg of investigational product was similar in the INF/SB2, INF/INF and SB2/SB2 groups (table S1 in online supplementary appendix).

Efficacy

The time–response pattern of mean DAS28, SDAI and CDAI in this transition study population is shown in figure 2. The pattern of disease activity improvement was highly similar among the three treatment groups during the entire study period. Figure 3 and table S2 (see online supplementary appendix) show the ACR20, 50 and 70 response rates, which were comparable across the double-blind randomised and transition period. While a somewhat higher variance was observed, especially in patients initially treated with INF who either transitioned to SB2 or continued INF, this pattern was already evident during the pretransition period before rerandomisation (assessed retrospectively), and the overall pattern did not deviate meaningfully during the period after the switch. The proportion of EULAR responses classified as good or moderate was comparable at week 78 across the treatment groups (good: 32.9%–35.6% of patients; moderate: 50.5%–51.8% of patients; figure S2 in online supplementary appendix).

When considering efficacy after dose increase of INF was permitted (ie, week 30 and thereafter), the efficacy response pattern was comparable among the three treatment groups, both in patients who had received at least one dose increment and in those who did not receive any dose increments (figure S3 in online supplementary appendix). Patients who needed at least one dose increment of INF or SB2 had experienced lower response rates than patients who did not have a dose increment, and patients who had a dose increment experienced an increase in efficacy across treatment groups. Such response patterns were generally consistent before and after rerandomisation (week 54). At week 78, patients who did not receive any dose increment and who had transitioned from INF to SB2 had a numerically lower ACR20 response rate than those who did continue treatment with either INF or SB2 throughout the entire study (figure S3 in online supplementary appendix). Thus, some variance in response pattern was observed in the INF/SB2 treatment group, which is thought to be a reflection of the overall efficacy pattern seen in figure 3.

Safety

The overall incidence of TEAEs reported during the transition period in the Ex-SAF population was comparable in each treatment group (table 2). The most commonly reported TEAEs during this period were latent tuberculosis, nasopharyngitis and RA (worsening); there were no deaths or new cases of active tuberculosis during the transition period. Three cases of malignancy were reported during the transition period: lip and/or oral cavity cancer and basal cell carcinoma in the INF/SB2 group and papillary thyroid cancer in the INF/INF group. Rates of serious TEAEs, serious infections and infusion-related reactions were low and comparable across the three treatment groups (table 2). There were four serious infections reported: two events in the INF/SB2 treatment group of arthritis bacterial and haematoma infection, one event in the INF/INF treatment group of respiratory tract infection and one event in the SB2/SB2 treatment group of urosepsis.

Immunogenicity

The incidence of overall ADA after transition and newly developed ADA after transition was comparable in the three treatment groups (figure 4). The incidence of overall positive ADA during the transition period among patients with overall negative ADA up to week 54 was 14.6% for INF/SB2, 14.9% for INF/INF and 14.1% for SB2/SB2 (NAb 33.3%, 71.4% and 63.6%) indicating that immunogenicity after switching from INF to SB2 was similar to that from continuing either INF or SB2.

DISCUSSION

Here we report results from the transition period of the phase III study of the INF biosimilar, SB2, in patients with moderate-to-severe RA despite methotrexate treatment. Our main goal was to demonstrate clinical comparability of switching from INF to SB2 with both ongoing reference INF as well as SB2. This type of comparative approach may be considered unique in INF biosimilar studies done hitherto; for example, switching of

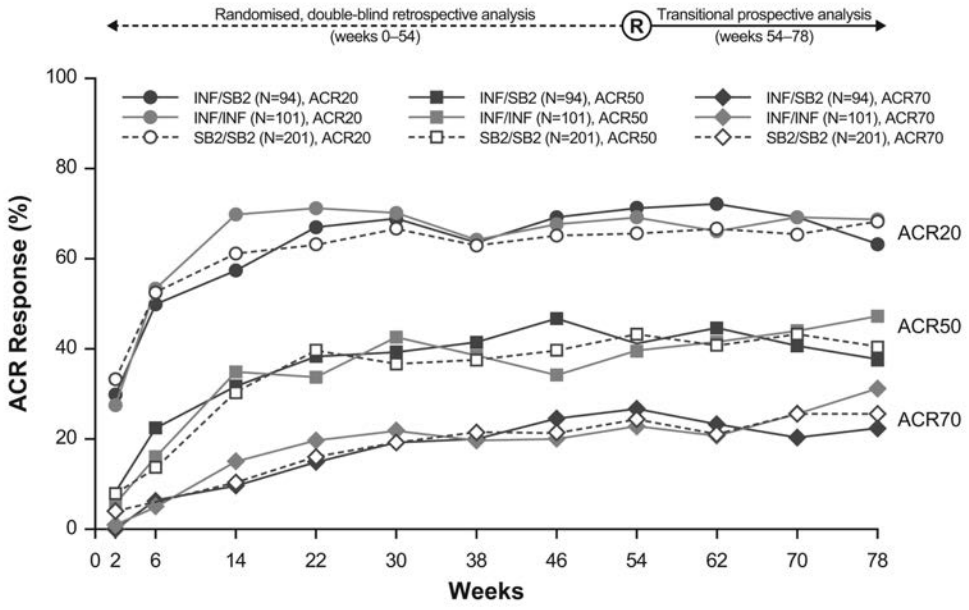


Figure 3 American College of Rheumatology (ACR) responses up to week 78. The responses before week 54 are retrospective analyses based on the extended full analysis set. For the actual percentages, please refer to online supplementary appendix table S2. INF, reference infliximab.

INF to CT-P13 was compared with continuing CT-P13, but not with a parallel, continuing reference INF arm.[19]

When switched from INF to SB2, there was no clinically meaningful difference in terms of efficacy, safety and immunogenicity compared with the INF/INF group. Likewise, the SB2/SB2 group also maintained long-term efficacy, safety and immunogenicity, again comparable with that of the long-term INF/INF group or the INF/SB2 group. Even dose increment patterns after week 54 were comparable among the three treatment groups, with a similar efficacy response. These results are consistent with our previous reports of SB2[8 17] but provide additional insight on switching and longer term treatment. Also, our study is unique among INF biosimilar studies in that it employed a switching design and continued with dose increments, both of which can be situations encountered in the clinical setting.

Our data showing that switching from originator to biosimilar is safe and effective are corroborated by the recent observations in the NOR-SWITCH and DANBIO study.[19 20] In the NOR-SWITCH study, efficacy and safety in patients with multiple diagnoses who were switched from reference INF to biosimilar CT-P13 were compared with those maintaining reference INF, revealing similar results, while in the DANBIO study, prior INF-receiving patients were non-medically switched to CT-P13 due to national policy yet maintaining similar disease activity compared with historical INF data. In both studies, comparison with a continuing biosimilar could not be tested, because it had not been available prior to initiation of the trial or non-medical switch.[19 20]

Recently, various study designs have been proposed to address the issue of biosimilar switching. Early switching designs employed a total group switch in which the originator treatment group was switched entirely to the biosimilar and compared with the ongoing biosimilar treatment group.[21 22] Others employed a multiple switch design, switching back and forth in both the originator and biosimilar treatment groups.[23] Our study design split the originator treatment arm into two groups and switched one of these groups to the biosimilar. While it is not clear which design is best for assessing biosimilar switching, our study allows simultaneous comparison of the switched group with both the ongoing originator and biosimilar groups, respectively, as mentioned previously.

Another important factor in switching designs is maintenance of study blinding. Because patients might exhibit different

Table 2 Summary of safety profile during the transition period

	INF/SB2 (n=94)	INF/INF (n=101)	SB2/SB2 (n=201)
At least one TEAE	34 (36.2)	36 (35.6)	81 (40.3)
Frequently reported TEAEs (≥2% in any treatment group)			
Latent tuberculosis	7 (7.4)	4 (4.0)	11 (5.5)
Nasopharyngitis	2 (2.1)	4 (4.0)	11 (5.5)
Rheumatoid arthritis	2 (2.1)	4 (4.0)	7 (3.5)
ALT increased	4 (4.3)	1 (1.0)	5 (2.5)
AST increased	4 (4.3)	2 (2.0)	4 (2.0)
Upper respiratory tract infection	3 (3.2)	5 (5.0)	1 (0.5)
Bronchitis	1 (0.5)	2 (2.0)	5 (2.5)
Pharyngitis	2 (2.1)	0 (0.0)	1 (0.5)
Tonsillitis	2 (2.1)	1 (1.0)	0 (0.0)
Headache	2 (2.1)	0 (0.0)	1 (0.5)
Antinuclear antibody positive	0 (0.0)	2 (2.0)	0 (0.0)
Any serious TEAE	6 (6.4)	3 (3.0)	7 (3.5)
Serious infection	2 (2.1)	1 (1.0)	1 (0.5)
Infusion-related reaction*	3 (3.2)	2 (2.0)	7 (3.5)
Malignancy†	2 (2.1)	1 (1.0)	0 (0.0)

Values represent n (%) of patients. Latent tuberculosis was diagnosed as having a newly positive QuantiFERON test that was negative at week 0.
*There were two serious infusion-related reactions (drug hypersensitivity in INF/SB2 group, anaphylactic reaction in SB2/SB2 group), which led to discontinuation of the investigational product.
†See text for details.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; INF, reference infliximab; TEAE, treatment-emergent adverse event.

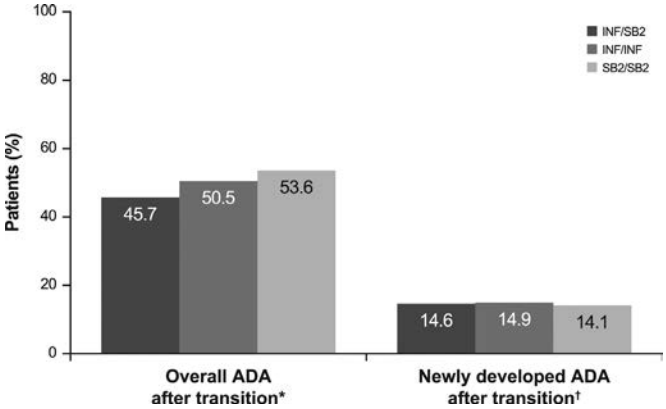


Figure 4 Incidence of immunogenicity during the transition period. *Patients having at least one positive ADA result during the transition-extension period among all patients regardless of prior ADA result up to week 54 (n=94 in INF/SB2, n=101 in INF/INF, n=201 in SB2/SB2). †Patients having at least one positive ADA result during the transition period among patients with overall negative ADA results up to week 54 (n=41 in INF/SB2, n=47 in INF/INF, n=78 in SB2/SB2). NAb was measured among ADA positive subjects (n=6, 7 and 11). ADA, antidrug antibody; NAb, neutralising antibody; INF, reference infliximab.

attitudes when becoming aware of receiving a biosimilar, this could potentially affect the study outcomes. Such 'nocebo' effects have been reported with chemical generic drug switching.[24] To avoid these effects, our study was fully blinded throughout, even including mock-randomisation procedures for the SB2/SB2 treatment group that did not change during the entire study period, thus minimising possible bias.

As a limitation of our study, because the INF population was split into two groups, the sample size for each treatment group decreased by half. This may have increased the potential for greater variation in clinical outcomes, possibly making comparisons between the treatment groups somewhat more difficult. This is suggested by the wider efficacy fluctuations seen in the INF/SB2 and INF/INF groups compared with the more stable pattern seen in the SB2/SB2 group; however, this variability already existed in the pretransition period on post hoc analysis. Thus, it is reassuring that despite such potential variations, the efficacy, safety and immunogenicity outcomes were comparable among the three treatment groups.

CONCLUSIONS

SB2, an INF biosimilar, maintained comparable efficacy, safety and immunogenicity up to 78 weeks, even after switching from the originator INF. Our results suggest that the clinical profile of SB2, when administered long term or when switched from INF, is comparable with INF.

Author affiliations
[1]Department of Rheumatology, Medical University of Vienna, Vienna, Austria
[2]Department of Internal Medicine, Catholic University of Daegu, School of Medicine, Daegu, South Korea
[3]Clinic of Internal Diseases, Department of Rheumatology and Clinical Immunology, Clinical Center Banja Luka, Banja Luka, Bosnia and Herzegovina
[4]Medica Pro Familia, Gdynia, Poland
[5]MHAT, Sliven, Bulgaria
[6]Medical Plus sro, Uherske Hradiste, Czech Republic
[7]Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic
[8]Department of Rheumatology, Lithuanian University of Health Sciences, Kaunas, Lithuania
[9]Internal Medicine #1 Department, SHEI Ivano-Frankivsk NMU, Ivano-Frankivsk, Ukraine
[10]University Clinic Centre Sarajevo, Sarajevo, Bosnia and Herzegovina
[11]Poznanski Osrodek Medyczny Novamed, Poznan, Poland
[12]Institute of Rheumatology and First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic
[13]MCBK S.C., GrodziskMazowiecki, Poland
[14]Medica Pro Familia Sp. z o.o. Spolka Komandytowo-Akcyjna, Warsaw, Poland
[15]Samsung Bioepis Co., Ltd, Incheon, Korea

Acknowledgements The authors would like to thank the patients who were involved in this study, the study personnel who made this work possible and the study investigators: Bosnia and Herzegovina: Sokolovic S; Bulgaria: Dimitrov E, Geneva-Popova M, Mihaylova M, Toncheva A, Penev D and Oparanov B; Czech Republic: Galatikova D, Vitek P and Janska L; Korea, Republic of: Shim SC, Kang YM, Kim HA, Kim SK, Lee S-H, Bae S-C, Kim J, Kwok S-K, Lee YJ and Lee S-K; Latvia: Kadisa A, Mihailova A, Saulite-Kandevica D and Saleniece S; Lithuania: Milasiene R, Arstikyte I and Basijokiene V; Poland: Kolczewska A, Stasiuk B, Grabowicz-Wasko B, Leszczynski P, Ruzga Z, Rychlewska-Hanczewska A and Hilt J; Romania: Mirea G, Pavel M, Ieremia G and Tanasescu C; Ukraine: Rekalov D, Zhdan V, Povoroznyuk V, Ter-Vartanian S, Stanislavchuk M, Golovchenko O, Tseluyko V, Yagensky A, Iaremenko O and Shevchuk S; and the study team: Ilsun Hong (Samsung Bioepis). Editorial support for development of this manuscript was provided by Michael S. McNamara at C4 MedSolutions, LLC (Yardley, Pennsylvania, USA), a CHC Group company, and funded by Samsung Bioepis Co., Ltd.

Contributors YL and YHR contributed to study conception and design, acquisition of data, analysis and interpretation of data, drafting the manuscript and revising it critically for important intellectual content and final approval of the version to be published. JSS contributed to acquisition of data, analysis and interpretation of data, drafting the manuscript and revising it critically for important intellectual content and final approval of the version to be published. J-YC, NP, JN, IS, ED, AB, RY, MM, WP, HC, KJ-R and AZ contributed to acquisition of data, drafting of the manuscript and revising it critically for important intellectual content and final approval of the version to be published. All coauthors contributed significantly to the writing of the manuscript.

Funding This study was funded by Samsung Bioepis Co., Ltd.

Competing interests JSS reports receiving grant/research support from AbbVie, Janssen, MSD, Pfizer, Roche and UCB; consultant for AbbVie, Amgen, AstraZeneca, Astro-Pharma, Celgene, GSK, Janssen, Lilly, Medimmune, MSD, Novartis-Sandoz, Novo Nordisk, Pfizer, Roche, Samsung Bioepis, Sanofi and UCB. J-YC reports receiving grant/research support and consultant fees from Samsung Bioepis. AB reports receiving grant/research support from AbbVie and Samsung Bioepis. NP, JN, IS, ED, RY, MM, WP, HC, KJ-R and AZ report receiving grant/research support from Samsung Bioepis. YL and YHR are employees of Samsung Bioepis and own stocks in Samsung Biologics.

Ethics approval Ethics approval was received from each national regulatory agency and central or local ethical committee.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Dörner T, Strand V, Cornes P, *et al*. The changing landscape of biosimilars in rheumatology. *Ann Rheum Dis* 2016;75:974–82.
2 Nam JL, Ramiro S, Gaujoux-Viala C, *et al*. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2014;73:516–28.
3 Putrik P, Ramiro S, Kvien TK, *et al*. Variations in criteria regulating treatment with reimbursed biologic DMARDs across European countries. Are differences related to country's wealth? *Ann Rheum Dis* 2014;73:2010–21.
4 Putrik P, Ramiro S, Kvien TK, *et al*. Inequities in access to biologic and synthetic DMARDs across 46 European countries. *Ann Rheum Dis* 2014;73:198–206.
5 Singh SC, Bagnato KM. The economic implications of biosimilars. *Am J Manag Care* 2015.
6 European Medicines Agency. Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf (accessed 12 Apr 2017).

7 US Food and Drug Administration. Guidance for industry. Scientific considerations in demonstrating biosimilarity to a reference product. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf (accessed 12 Apr 2017).
8 Choe JY, Prodanovic N, Niebrzydowski J, *et al*. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2017;76:58–64.
9 Emery P, Vencovský J, Sylwestrzak A, *et al*. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2017;76:51–7.
10 Yoo DH, Hrycaj P, Miranda P, *et al*. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis* 2013;72:1613–20.
11 Kay J. Editorial: biosimilars: new or deja vu? *Arthritis Rheumatol* 2016;68:1049–52.
12 Janssen Biologics B.V. *Summary of product characteristics*: Remicade. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf (accessed 28 Feb 2017).
13 Shin D, Kim Y, Kim YS, *et al*. A randomized, phase I pharmacokinetic study comparing SB2 and Infliximab reference product (Remicade(®)) in healthy subjects. *BioDrugs* 2015;29:381–8.
14 Hong J, Lee Y, Lee C, *et al*. Physicochemical and biological characterization of SB2, a biosimilar of Remicade® (infliximab). *MAbs* 2017;9:365–83.
15 European Medicines Agency. Summary of opinion (initial authorisation). Flixabi. Infliximab. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004020/WC500203991.pdf (accessed 12 Apr 2017).
16 Samsung Bioepis. *Samsung Bioepis' Biologics License Application for SB2 infliximabb*: Newsroom. http://www.samsungbioepis.com/en/newsroom/detail/Samsung-Bioepis-Biologics-License-Application-for-SB2-Infliximab-Biosimilar-Accepted-by-FDA.html (accessed 12 Apr 2017).
17 Smolen JS, Choe JY, Prodanovic N, *et al*. Comparing biosimilar SB2 with reference infliximab after 54 weeks of a double-blind trial: clinical, structural and safety results. *Rheumatology* 2017;56:1771-1779.
18 Anderson J, Caplan L, Yazdany J, *et al*. Rheumatoid arthritis disease activity measures: american college of rheumatology recommendations for use in clinical practice. *Arthritis Care Res* 2012;64:640–7.
19 Jørgensen KK, Olsen IC, Goll GL, *et al*. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet* 2017;389:2304–16.
20 Glintborg B, Sørensen IJ, Loft AG, *et al*. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. *Ann Rheum Dis* 2017;76:1426–31.
21 Yoo DH, Prodanovic N, Jaworski J, *et al*. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. *Ann Rheum Dis* 2017;76:355–63.
22 Emery P, Vencovský J, Sylwestrzak A, *et al*. Long-term efficacy and safety in patients with rheumatoid arthritis continuing on SB4 or switching from reference etanercept to SB4. *Ann Rheum Dis* 2017;76:1986–91.
23 Griffiths CEM, Thaçi D, Gerdes S, *et al*. The EGALITY study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis. *Br J Dermatol* 2017;176:928–38.
24 Weissenfeld J, Stock S, Lüngen M, *et al*. The nocebo effect: a reason for patients' non-adherence to generic substitution? *Pharmazie* 2010;65:451–6.

EXTENDED REPORT

Development of a consensus core dataset in juvenile dermatomyositis for clinical use to inform research

Liza J McCann,[1] Clarissa A Pilkington,[2,3] Adam M Huber,[4] Angelo Ravelli,[5] Duncan Appelbe,[6] Jamie J Kirkham,[6] Paula R Williamson,[6] Amita Aggarwal,[7] Lisa Christopher-Stine,[8] Tamas Constantin,[9] Brian M Feldman,[10] Ingrid Lundberg,[11] Sue Maillard,[2] Pernille Mathiesen,[12] Ruth Murphy,[13] Lauren M Pachman,[14,15,16] Ann M Reed,[17] Lisa G Rider,[18] Annet van Royen-Kerkof,[19] Ricardo Russo,[20] Stefan Spinty,[21] Lucy R Wedderburn,[2,3,22,23] Michael W Beresford[1,24]

Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-212141).

For numbered affiliations see end of article.

Correspondence to
Dr Liza J McCann, Department of Paediatric Rheumatology, Alder Hey Children's NHS Foundation Trust, Liverpool L14 5AB, UK;
liza.mccann@alderhey.nhs.uk

Received 27 July 2017
Revised 23 September 2017
Accepted 1 October 2017
Published Online First 30 October 2017

ABSTRACT

Objectives This study aimed to develop consensus on an internationally agreed dataset for juvenile dermatomyositis (JDM), designed for clinical use, to enhance collaborative research and allow integration of data between centres.

Methods A prototype dataset was developed through a formal process that included analysing items within existing databases of patients with idiopathic inflammatory myopathies. This template was used to aid a structured multistage consensus process. Exploiting Delphi methodology, two web-based questionnaires were distributed to healthcare professionals caring for patients with JDM identified through email distribution lists of international paediatric rheumatology and myositis research groups. A separate questionnaire was sent to parents of children with JDM and patients with JDM, identified through established research networks and patient support groups. The results of these parallel processes informed a face-to-face nominal group consensus meeting of international myositis experts, tasked with defining the content of the dataset. This developed dataset was tested in routine clinical practice before review and finalisation.

Results A dataset containing 123 items was formulated with an accompanying glossary. Demographic and diagnostic data are contained within form A collected at baseline visit only, disease activity measures are included within form B collected at every visit and disease damage items within form C collected at baseline and annual visits thereafter.

Conclusions Through a robust international process, a consensus dataset for JDM has been formulated that can capture disease activity and damage over time. This dataset can be incorporated into national and international collaborative efforts, including existing clinical research databases.

To cite: McCann LJ, Pilkington CA, Huber AM, *et al*. *Ann Rheum Dis* 2018;**77**:241–250.

INTRODUCTION

Juvenile dermatomyositis (JDM) is associated with significant morbidity and mortality.[1–3] To better understand this rare disease,[4] international collaboration is essential. This is feasible with the development of national and international electronic web-based registries and biorepositories.[5 6] For good clinical care and to aid comparison of data between groups, it is crucial to have a common dataset that clinicians and researchers collect in a standardised way, with items clearly defined. The International Myositis and Clinical Studies (IMACS) Group[7–9] and Paediatric Rheumatology International Trials Organisation (PRINTO)[10–12] JDM core sets were developed predominantly for research studies. Existing myositis registries include partially overlapping but different dataset items, making comparison between groups challenging.[13] This study aimed to define optimal items from existing datasets that would be useful to collect in routine practice, within accessible disease-specific registries, that, when measured over time, would help capture disease outcome/treatment response, which would facilitate both patient care and translational research.

METHODS

The study protocol and background work have been published.[13 14] The study is registered on the Core Outcome Measures in Effectiveness Trials initiative database.[15] The Core Outcome Set—STAndards for Reporting standards for reporting were followed.[16] The study overview is shown in figure 1.

Background work

A steering committee (SC) developed a prototype dataset by scrutinising all items within existing international databases of juvenile-onset myositis (JM) and adult-onset myositis,[1 17–19] informed by a literature search and detailed analysis of the UK Juvenile Dermatomyositis Cohort Biomarker Study and Repository (JDCBS).[13 19] Leading representatives of each partner organisation[9 12 17 20 21] detailed in the study protocol[14] approved the template/provisional dataset.

Stakeholder groups

This study design aimed to employ representation from healthcare professionals with experience in myositis working as physicians, allied health professionals or clinical scientists in paediatric or adult medicine within rheumatology, neurology or dermatology[14] and consumers (patients with JM and their parents or carers).

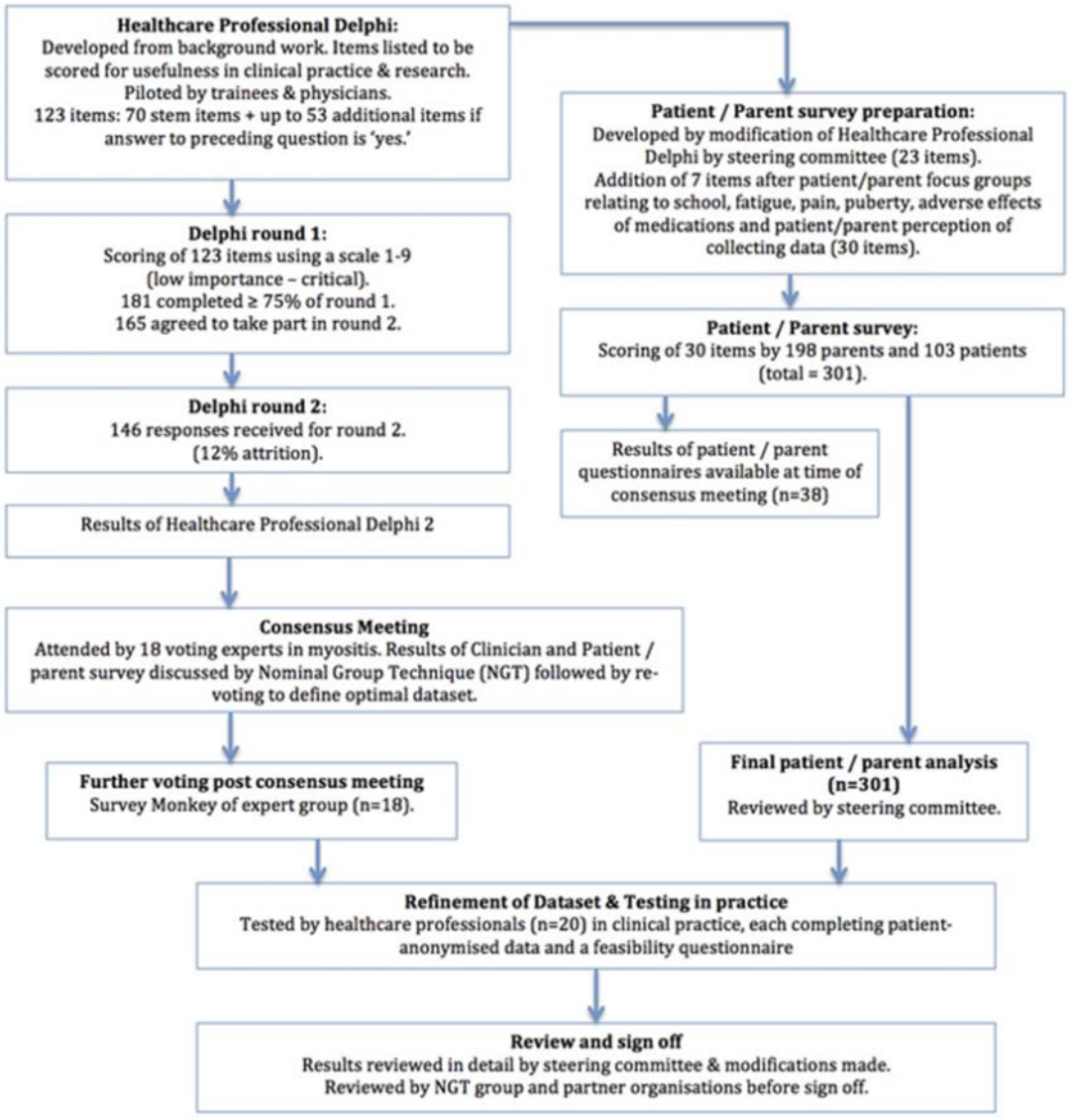


Figure 1 Flow chart showing study overview.

Healthcare professional Delphi process

A two-stage Delphi process was undertaken.[14] Items contained within the prototype dataset were listed and further modified by the SC to ensure clarity. The items were formatted into a custom-made electronic questionnaire, piloted before distribution. After modifications, the Delphi template included 70 items with an additional 53 conditional on previous response (detailed in online supplementary table S1). Participation was invited via membership lists of IMACS, Childhood Arthritis and Rheumatology Research Alliance (CARRA), Juvenile Dermatomyositis Research Group (JDRG) UK and Ireland, Paediatric Rheumatology European Society (PReS) JDM working party and PRINTO Centre Directors. These are representative of international paediatric rheumatology and myositis specialty groups, capturing opinion of clinicians, scientists and allied health professionals. The estimated membership of these groups totals more than 1000. However, the majority of members belong to more than one organisation and membership lists include retired/non-active members or specialists working in adult-onset myositis potentially less inclined to answer a paediatric-specific survey.[14] Participants were asked to rate the importance of each item for clinical practice and separately for value in research, using a scale of 1–9: 1–3 (of low importance), 4–6 (important but not critical) and 7–9 (critical).[14] An option of 'unable to score' was given and free text comments were allowed. Delphi 2 was sent to participants who scored 75% or more of the items in round 1 of the Delphi. Each participant was asked to re-score each item, having been shown the distribution of scores for the group as a whole and their own score.

Patient and parent survey

The healthcare professionals' survey was modified into separate parent and patient questionnaires as per protocol,[14] formatted for computer or paper format completion. The questionnaires and age-appropriate information leaflets were reviewed by patient and public involvement coordinators and by parent/young people's focus groups.[14] The focus groups also reviewed patient/parent-reported outcome measures (PROMs) used for JDM and other rheumatology conditions,[22–27] and opinions were summarised (online supplementary table S2). Thirty items were included in patient/parent questionnaires; 23 from adaptation of the Delphi (combining or simplifying items from the healthcare professional questionnaire and selecting items

Table 1 Definition of consensus for each stage of the study (defined a priori)

Consensus classification	Description	Definition of consensus		
		Healthcare professionals' Delphi	Patient/parent survey	Consensus meeting*
Consensus in	Consensus that outcome should be included in core set	≥70% of participants scoring '7–9' 'critical for decision-making'	≥70% of participants scoring 'really important'	≥80% of participants voting for inclusion in core outcome set
Consensus out	Consensus that outcome should not be included in the core outcome set	≥70% of participants scoring '1–3' 'low importance'	≥70% of participants scoring 'not that important'	<80% of participants voting for inclusion in core outcome set
Equivocal	Uncertainty about importance of outcome	All other responses	All other responses	Further discussion by NGT and re-voting allowed

*More stringent consensus cut-off for consensus meeting.
NGT, nominal group technique.

particularly relevant to patients/parents), 2 additional questions added by the SC to determine patient/parent perspectives on collecting and storing information, plus 5 questions suggested by patients/parents within focus groups (online supplementary table S1). The scoring system was simplified into three categories of 'not that important', 'important' and 'really important'. An option of 'unable to score' was given and free text comments were allowed. Participation was open to any patient with JM—child/adult, or any parent/carer of a child with JM. Patients with adult-onset myositis (onset ≥18 years) were excluded. Information leaflets and questionnaires were in English only; translators could be used if available. Patients/parents were signposted to the study via email distribution lists/websites of North American and UK patient support groups (Cure JM and Myositis UK),[28 29] the lead of the JDRG patient/parent groups and JDRG coordinator.[20] In addition, following site-specific ethics approval, UK centres participating in the JDCBS[19 30] and a Netherlands site invited patients/parents to participate.

Data analysis

For each item, the number and percentage of participants who scored the item and the distribution of scores (grades 1–9) were summarised for each stakeholder group. Consensus definitions were applied as 'consensus in' versus 'equivocal' or 'consensus out' according to predefined consensus definitions (table 1).

Consensus meeting

Eighteen voting delegates were invited to a 2-day consensus meeting, led by a non-voting facilitator (MWB). International representatives were experts in myositis from paediatric rheumatology/myositis groups and professionals who care for patients with myositis including neurologists, dermatologists, adult rheumatologists and physiotherapists. Prior to the meeting, delegates were sent a summary of results to review. During the consensus meeting, Delphi 2 results and patient/parent results were presented for each item—as shown in online supplementary figure 1. Items achieving 'consensus in' within the Delphi and patient/parent questionnaires were voted on immediately. Those not achieving 'consensus in' were discussed by nominal group technique. Consensus was defined a priori as ≥80% (table 1). Discussion and re-voting allowed refinement of items or associated definitions. The process continued until consensus was reached or until it was clear that consensus would not be reached.

Testing in practice

The proposed dataset was formatted into three sections (forms A, B and C) and tested in clinical practice. Members of the expert group were asked to test the dataset themselves and/or delegate a member of their department unfamiliar with the dataset. Clinicians completed patient-anonymised data on one to two patients under their care and a feasibility questionnaire (online supplementary table S3). Feedback was considered by the SC and refinements made. The dataset was sent to the expert group, including representatives of partner organisations (IMACS, CARRA, PRINTO, PReS JDM working group, JDRG, Euromyositis) for comment.

RESULTS

Two hundred and sixty-two healthcare professionals accessed the system (26% of the estimated total membership of specialty groups). 181/262 (69%) completed ≥75% of Delphi 1 (June–September 2014). One hundred and sixty-five agreed to take part in Delphi 2 (November 2014–January 2015); from these, 146 replies were received (12% attrition). One hundred and seventy-two participants provided full demographic data in round 1 showing that survey responses were received from Europe (44%), North America (34%), Latin America (12%), Asia (6%), Australia/Oceania (0.5%), Middle East (3%) and Africa (0.5%). Respondents primarily were paediatric or adult rheumatologists (85%) or had an interest in rheumatology (8%), but also included clinical academics (specialty not defined, 4%), dermatologists (0.5%), neurologists (0.5%), physiotherapists (1%) or other professionals (1%). The majority of respondents had substantial experience in the specialty (74% with ≥10 years of experience) and worked within paediatrics/mainly paediatrics (82.5% vs 17.5% of respondents working with adults). Responses were summarised as percentages of participants ranking items as critical for decision-making (score 7–9) for each item (clinical/research), shown in online supplementary table S1. Availability of investigations to clinicians within clinical practice was also summarised from responses received in Delphi 1 (online supplementary table S4 and online supplementary figure S1).

Patient/parent surveys

In total, 301 surveys were completed (198 from parents, 103 patients). To allow time for sufficient data capture for parent/patient questionnaires, data collection continued after the consensus meeting. At the consensus meeting, data were available from 16 completed patient surveys and 22 parent surveys. Decisions made at the consensus meeting with 38 responses still held true in the final analysis of 301 replies. Responses were received from Europe (53%), North America (44%) and other continents (3%). Patients completing the questionnaire were a median of 15 years of age (IQR 12–17). Parents completed questionnaires for children who had a median age of 11 years (IQR 7–15). Overall, there was good agreement between patient/parent surveys and the healthcare professionals' Delphi and items agreed at the consensus meeting (online supplementary table S1). Key exceptions are summarised in table 2.

Table 2 Key differences between opinions of patients/parents and healthcare professionals

Item	Patients' opinion	Parents' opinion	Healthcare professionals' opinion	Outcome from consensus meeting	Comments/reasons for retaining in dataset
Raynaud's phenomenon	Equivocal	Equivocal	Consensus in	Consensus in	Important for overlap phenotypes especially myositis–scleroderma
Use of an age-appropriate patient/parent measure of function	Equivocal	Equivocal	Consensus in	Consensus in	Retained (with the option of using alternative tools to allow for country-specific requirements) since these are standard outcome measures for research in JDM
Use of an age-appropriate patient/parent measure of quality of life	Equivocal	Equivocal	Consensus in	Consensus in	
Parent/patient global assessment VAS	Equivocal	Equivocal	Consensus in	Consensus in	
Physician global assessment VAS	Equivocal	Equivocal	Consensus in	Consensus in	
Fatigue due to myositis (within PROM)	Equivocal	Consensus in	Consensus in	Consensus in—as part of a PROM	Quantifiable outcome measure
Questions related to physiotherapy	Equivocal	Equivocal	Consensus in	Consensus in	Increasingly a defined therapeutic intervention; omitting would be akin to not asking about medicines
Pubertal assessment	Equivocal	Equivocal	(Not asked)*	Consensus in	Important outcomes of disease activity/damage/adverse effects of medication
Height of patient	Equivocal	Consensus in	Consensus in	Consensus in	
Weight of patient	Equivocal	Consensus in	Consensus in	Consensus in	
Items related to major organ involvement—cardiac/pulmonary/gastrointestinal	Equivocal	Consensus in	Consensus in	Consensus in	Important implications for disease severity, treatment and prognosis
Specific questions about pain	Consensus in	Consensus in	(Not asked)	Consensus out	Thought to be part of standard care (questions that would be asked by a clinician in a clinic consultation)
Specific questions about medicines	Consensus in	Consensus in	(Not asked)	Consensus out	
Irritability due to JDM	Equivocal	Consensus in	(Not asked)	Consensus out	Too non-specific and variable interpretation in different countries

*Added to patient/parent questionnaire after discussion in patient/parent focus groups.
JDM, juvenile dermatomyositis; PROM, patient/parent-reported outcome measure; VAS, Visual Analogue Scale.

Consensus meeting and output

All invited experts (n=18) attended the consensus meeting (Liverpool, March 2015), representing Europe (n=10), North America (n=6), Latin America (n=1) and Asia (n=1). Specialties included paediatric rheumatology (n=13), adult rheumatology (n=2), paediatric dermatology (n=1), paediatric neurology (n=1) and physiotherapy (n=1). Parents/patients were not included. Output from the consensus meeting is shown in online supplementary table S1. A set of recommendations for first visit, for each visit and for annual assessment was made. Refinement took place following the consensus meeting via three rounds of SurveyMonkey, principally to better define myositis overlap features and disease damage items (shown in online supplementary table S1), with the same members of the expert group (100% response rate).

Testing the dataset in practice

Glossaries of definitions/instructions to aid completion, along with muscle strength-testing sheets, were formulated into appendices, approved by the SC. Twenty clinicians tested the dataset (October 2016–April 2017); eight were present at the consensus meeting, three had completed the Delphi and nine were new to the dataset. Time taken to complete the dataset in clinical practice ranged from 5 to 45 min (median time 15 min).

Table 3 Summary of items included in the JDM optimal dataset, form A (completed at first/baseline visit only)

Section heading	Items		Additional items conditional on previous response (summary)
Personal factors/demographics	1	Date of birth (year and month of birth±day of birth)	
	2	Sex of patient	
Diagnostic factors	3	Date (year and month) of first symptom of myositis	
	4	Date (year and month) of diagnosis of JDM	
	5	At the time of diagnosis did the patient have proximal muscle weakness?	
	6	At the time of diagnosis did the patient have typical skin features of JDM (Gottron's/heliotrope)?	
	7	Was an MRI scan done at diagnosis?	Choice of options for MRI result (four options)
	8	Was a muscle biopsy done at diagnosis?	Choice of options for biopsy result (four options plus total biopsy score if available)
	9	Were myositis-specific antibodies tested at diagnosis?	If positive, asked to select all that apply (eight options)
	10	Were myositis-associated antibodies tested at diagnosis?	If positive, asked to select all that apply (nine options)
Treatments received prior to diagnosis of JDM	11	Did this patient receive systemic glucocorticoid prior to diagnosis of JDM?	If yes, asked to select all that apply (three options)
	12	Did this patient receive any synthetic or biologic disease modifying anti-rheumatic drug prior to the diagnosis of JDM?	If yes, asked to select all that apply (13 options)

JDM, juvenile dermatomyositis.

Table 4 Summary of items included in the JDM optimal dataset, form B (completed at every visit representing status of the patient at the current time point)

Section heading	Items		Additional items conditional on previous response (summary)
Growth	1	Height of patient (in centimetres)	
	2	Weight of patient (in kilograms)	
Muscular involvement	3	Presence of symmetrical proximal muscle weakness	
	4	Childhood Myositis Assessment Scale score	State score (out of 52)
	5	Manual Muscle Testing score	State score (out of 80)
	6	VAS score for global muscle disease activity	If measured, mark score on 10 cm line*
Skeletal involvement	7	Arthritis due to myositis	
	8	Joint contractures due to myositis	
	9	VAS score for global skeletal disease activity	If measured, mark score on 10 cm line*
Cutaneous involvement	10	Gottron's papules or Gottron's sign	
	11	Heliotrope rash	
	12	Periungual capillary loop changes (plus measure of capillary density if available)	
	13	Malar or facial erythema	
	14	Linear extensor erythema	
	15	'V' sign	
	16	Shawl sign	
	17	Non sun-exposed erythema	
	18	Extensive cutaneous erythema, which may include erythroderma	
	19	Livedo reticularis	
	20	Cutaneous ulceration	
	21	Mucus membrane lesions	
	22	Mechanic's hands	
	23	Cuticular overgrowth	
	24	Subcutaneous oedema	
	25	Panniculitis	
	26	Alopecia (non-scarring)	
	27	Calcinosis (with active disease)	
	28	VAS score for global cutaneous disease activity	If measured, mark score on 10 cm line*
Features suggestive of myositis overlap	29	Does this patient have a myositis overlap condition?	If yes, asked to select all that apply (four options)
	30	Raynaud's phenomenon	
	31	Sclerodactyly	
Gastrointestinal involvement	32	Dysphagia due to myositis	
	33	Abdominal pain due to myositis	
	34	Gastrointestinal ulceration due to myositis	
	35	VAS score for global gastrointestinal disease activity	If measured, mark score on 10 cm line*
Pulmonary involvement	36	Pulmonary involvement/respiratory muscle weakness or interstitial lung disease due to myositis	
	37	Dysphonia due to myositis	
	38	VAS score for global pulmonary disease activity	If measured, mark score on 10 cm line*
Cardiovascular involvement	39	Cardiovascular involvement due to myositis	
	40	BP recording	State systolic and diastolic measurement
	41	BP elevated suggesting hypertension (for age of patient)	
	42	VAS score for global cardiovascular disease activity	If measured, mark score on 10 cm line*
Constitutional features	43	Fever (>38°C) due to myositis	
	44	Weight loss (>5%) due to myositis	
	45	Fatigue due to myositis	
	46	VAS score for global constitutional disease activity	If measured, mark score on 10 cm line*
Global disease assessment by clinician	47	Physician VAS score of global disease activity	If measured, mark score on 10 cm line*
	48	Physician VAS score of extramuscular disease activity	If measured, mark score on 10 cm line*
Global disease assessment by patient/parent	49	Patient/parent VAS score for global disease activity	If measured, mark score on 10 cm line* and state who completed (four options)
	50	Patient/parent VAS score for pain	If measured, mark score on 10 cm line*
PROM	51	Use of an age-appropriate PROM of function	Asked to state PROM used and score
	52	Use of an age-appropriate patient/parent-reported measure of quality of life	Asked to state PROM used and score

Continued

Table 4 Continued

Section heading	Items		Additional items conditional on previous response (summary)
Investigations	53	Elevation of any muscle enzyme (including CPK, LDH, aldolase, AST/SGOT, ALT/SGPT) above normal range	If elevated, asked to select which apply (five options)
Specimens available	54	Has this patient had specimens taken that may be available for specific research projects? This may include DNA, serum, biomarkers, biopsy tissue or other material	If answer is 'yes', asked to select which apply (three options)
Treatment	55	Is the patient on treatment (now or since last visit)?	Asked to select all that apply (16 options) and to state dose, route and frequency for each medication
	56	Is the patient doing a regular exercise routine prescribed by a healthcare professional aimed at improving/maintaining: (A) range of movement? (B) muscle strength?	

*0 is inactive or lowest score and 10 is most active or highest score on 10 cm VAS scores.
ALT, alanine transaminase; AST, aspartate aminotransferase; BP, blood pressure; CPK, creatine phosphokinase; JDM, juvenile dermatomyositis; LDH, lactate dehydrogenase; PROM, patient/parent-reported outcome measure; SGOT, serum glutamic oxaloacetic Transaminase; SGPT, serum glutamic-pyruvic transaminase; VAS, Visual Analogue Scale.

In addition, 15/20 (75%) found the dataset helpful in practice. Feedback was reviewed in detail by the SC and refinements made.

Completed optimal dataset

The resulting optimal dataset is summarised within tables 3–5 representing three forms. They consist of 123 items: 12 (plus 6 items conditional on responses to the initial 12) within form A, to be completed at first/baseline data entry only; 56 (plus 20 conditional on responses to the 56) within form B, to be completed at every clinic visit representing status of the patient at the current time point; and 55 (plus 15 conditional on responses to the 55) within form C, to be completed at baseline and then annually to capture disease damage. The complete dataset with glossary of definitions and muscle strength-testing sheets can be found in the website of University of Liverpool (http://ctrc.liv.ac.uk/JDM/) and online supplementary table S5.

DISCUSSION

An internationally agreed JDM dataset has been designed for use within a clinical setting, with the potential to significantly enhance research collaboration and allow effective communication between groups. The accompanying glossary of definitions may be particularly helpful to those in training or physicians less familiar with JDM and for standardisation of the information. Key items are included within the dataset that allow documentation of disease activity and damage with the ability to measure change over time. If adopted widely, the dataset could enable analysis of the largest possible number of patients with JDM to improve disease understanding. It is anticipated that further ratification of the dataset will take place when incorporated into existing registries and national/international collaborative research efforts. It is acknowledged that updates may be needed in the future to incorporate advances in JDM.

When tested in practice by a small number of clinicians, the forms took between 5 and 45 min to complete. The wide range is likely to be due to some respondents interpreting this question as time taken to complete the actual forms, while others may have documented time taken to complete all the tasks within the forms, including clinical examination. It is likely that completion time will be reduced as clinicians become familiar with the questions over time and employment of electronic data entry systems. The dataset does not encompass every aspect of a clinic consultation. Other factors such as adverse effects to medication or details of pain (ranked important by patients/parents) should be covered as part of standard care.

This study has benefited from the enormous contribution of patients and parents. It is interesting that patients do not necessarily perceive items such as shortness of breath, chest pain and abdominal symptoms as important in JDM whereas for clinicians, major organ involvement has important implications for prognosis and treatment choices.[31–37] Likewise, growth and pubertal parameters were rated less important by patients/parents but retained due to impact of active disease and corticosteroid treatment on growth.[38 39] Self-assessment is allowable to make pubertal assessment more acceptable to patients.[40] Notable discrepancies in healthcare professional and patient/parent opinion included the use of PROMs capturing function and health-related quality of life (HRQOL). The benefits and limitations of individual tools have been described.[22 27] Within this study, comments from patient/parent surveys and focus groups suggested a dislike of 0–10 cm scales used in VAS measurements (data not shown). It is possible that a pain/general VAS is not adequate to capture the complexity of pain or overall feelings for a patient, particularly due to the variability of the disease. Despite this caveat, clinicians recognise the need to have outcome-driven data that include measures of activity, participation, pain and HRQOL.[27] Patients with JDM have been found to have significant impairment in their HRQOL compared with healthy peers.[41] PROMs used within the IMACS and PRINTO core sets, including the Childhood Health Assessment Questionnaire and Child Health Questionnaire, are not designed specifically for JDM but have been evaluated and endorsed for use in juvenile myositis.[22] The Juvenile Dermatomyositis Multidimensional Assessment Report (JDMAR) is a multifunctional tool that includes function, quality of life, fatigue and adverse effects of medications that has been specifically developed for JDM.[23] It is currently undergoing further validation. Fatigue, rated as important by parents in this work, is included within the JDMAR. During the consensus meeting, it was not possible to define a single agreed PROM for function (activity) or HRQOL (participation) despite taking into consideration results of the healthcare professionals' Delphi, patient/parent surveys and feedback from patients within a UK focus group (online supplementary table S2). The difficulty of PROMs being internationally accepted was discussed and noted. Specifically, items within tools developed in Europe/North America may not be relevant in economically less developed countries. It was agreed that the dataset would include a recommendation to use 'an age-appropriate patient/

Table 5 Summary of items included in the JDM optimal dataset, form C (completed at baseline visit and then annual visits only)

Section heading	Items		Additional items conditional on previous response (summary)
Muscular damage items	1	Muscle atrophy (clinical)	
	2	Muscle weakness not attributable to active muscle disease	
	3	Muscle dysfunction: decrease in aerobic exercise capacity	
	4	VAS for global muscle disease damage	Mark score on 10 cm line*
Skeletal damage items	5	Joint contractures (due to myositis)	
	6	Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	
	7	Avascular necrosis	
	8	Deforming arthropathy	
	9	VAS for global skeletal disease damage	Mark score on 10 cm line*
Cutaneous damage items	10	Calcinosis (persistent)	
	11	Alopecia (scarring)	
	12	Cutaneous scarring or atrophy (depressed scar or cutaneous atrophy)	
	13	Poikiloderma	
	14	Lipoatrophy/lipodystrophy	
	15	VAS for global cutaneous disease damage	Mark score on 10 cm line*
Gastrointestinal damage items	16	Dysphagia (persistent)	
	17	Gastrointestinal dysmotility, constipation, diarrhoea or abdominal pain (persistent)	
	18	Infarction or resection of bowel or other gastrointestinal organs	
	19	VAS for global gastrointestinal disease damage	Mark score on 10 cm line*
Pulmonary damage items	20	Dysphonia (persistent)	
	21	Impaired lung function due to respiratory muscle damage	
	22	Pulmonary fibrosis	
	23	Pulmonary hypertension	
	24	VAS for global pulmonary disease damage	Mark score on 10 cm line*
Cardiovascular damage items	25	Hypertension requiring treatment for >6 months	
	26	Ventricular dysfunction or cardiomyopathy	
	27	Assessed in adults (>18 years of age) only: angina or coronary artery bypass	
	28	Assessed in adults (>18 years of age) only: myocardial infarction	
	29	VAS for global cardiovascular damage	Mark score on 10 cm line*
Peripheral vascular damage items	30	Tissue or pulp loss	
	31	Digit loss or limb loss or resection	
	32	Venous or arterial thrombosis with swelling, ulceration or venous stasis	
	33	Assessed in adults (>18 years of age) only: claudication	
	34	VAS for global peripheral vascular disease damage	Mark score on 10 cm line*
Pubertal status of patient	35	Pubertal assessment completed by physician or by patient (self-assessment)	Tanner score (1–5)
Endocrine damage items	36	Growth failure	
	37	Delay in development of secondary sexual characteristics (>2 SD beyond mean for age)	
	38	Hirsutism or hypertrichosis	
	39	Irregular menses	
	40	Primary or secondary amenorrhoea	
	41	Diabetes mellitus	
	42	In adults (>18 years of age): infertility—male or female	
	43	In adults (>18 years of age): sexual dysfunction	
	44	VAS for global endocrine disease damage	Mark score on 10 cm line*
Ocular damage items	45	Cataract resulting in visual loss	
	46	Visual loss, other, not secondary to cataract	
	47	VAS for global ocular disease damage	Mark score on 10 cm line*
Infection damage items	48	Chronic infection	
	49	Multiple infections	
	50	VAS for global infection damage	Mark score on 10 cm line*
Malignancy	51	Presence of malignancy	
	52	VAS for malignancy (complications)	Mark score on 10 cm line*
Other damage	53	Death	Include cause and date of death
	54	VAS for any other damage	Mark score on 10 cm line* and add details of other damage
Global disease assessment damage	55	Physician VAS of global disease damage	Mark score on 10 cm line*

*0 is inactive or lowest score and 10 is most active or highest score on 10 cm VAS scores.
JDM, juvenile dermatomyositis; VAS, Visual Analogue Scale.

parent-reported outcome of function' and 'an age-appropriate patient/parent-reported measure of quality of life'. More work is needed to make PROMs acceptable to patients/parents and applicable to their disease.[42 43]

This study is limited by the fact that patient/parent questionnaires were available in English only, reducing the number of countries that could contribute; hence, there is low patient participation outside of Europe and the USA. Complete data from patient/parent surveys were not available at time of the consensus meeting. However, reanalysis of outcomes after the close of the patient/parent survey showed that decisions made at the consensus meeting still held. Initial response rate to Delphi 1 was low (estimated at 26% of potential specialty group membership). However, not all members of the respective organisations contacted would be expected to answer a paediatric-specific survey as described previously. Response rates and attrition between Delphi 1 and 2 were as expected from paediatric rheumatology studies with similar methodology.[44–46] Despite inclusion of neurology and dermatology experts in the consensus meeting, the participants of this study were primarily rheumatologists.

Considerable discussion took place during the consensus meeting regarding the assessment of cutaneous disease in myositis. There are many tools available,[22] but no single tool has been universally accepted. It can be difficult to define skin activity versus damage, particularly without a skin biopsy. After voting on individual skin items and comparing two tools endorsed in JDM, the abbreviated Cutaneous Assessment Tool (aCAT) and Disease Activity Score (DAS) skin score,[22] agreement was reached to use items within the aCAT as disaggregated skin manifestations. These items are recognised to reflect cutaneous lesions associated with disease activity and damage in juvenile and adult myositis.[22] Within the item 'periungual capillary loop changes', 'measure of nailfold capillary density if available' was added in recognition of nailfold density relating to prognosis.[47 48] A direct comparison of all available skin tools was outside the remit of this study. Recent published work evaluating the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) and the Cutaneous Assessment Tool Binary Method (CAT-BM) in JDM confirms the reliability of both tools when used by paediatric dermatologists or rheumatologists.[49]

The consensus-driven dataset developed in this study, like IMACS and PRINTO core sets, includes physician and patient/parent global activity, each of which is included in recently defined response criteria for minimal, moderate and major improvement in JDM.[8] IMACS measures muscle strength using Manual Muscle Testing, whereas CMAS is used within the PRINTO core set. Both were retained in the consensus dataset. Both tools have been found to have very good inter-rater reliability (when summary scores are used)[22] and either is allowed in the recently defined American College of Rheumatology/European League Against Rheumatism–approved response criteria.[8] The overlap between the IMACS/PRINTO core sets and items contained within the consensus dataset is unsurprising as all core sets aim to capture and measure disease activity and damage over time. A key difference is that the consensus dataset does not use specific tools to record disease activity, such as the Myositis Disease Activity Assessment Tool or the DAS, but rather uses disaggregated items, each of which has been evaluated by a multistage consensus-driven process that considered value for both clinical use and research. The dataset was developed with a key aim for it to be incorporated into existing registries, allowing comparison of data between groups. The already available web-based Euromyositis registry, www.euromyositis.eu, is free to use in clinical practice and for research and includes a JDM proforma, which will be modified where needed to include items in this new dataset. Likewise, at the time of writing, the CARRA Registry is in the final stages of adding JDM (https://carragroup.org/) and will include the items contained in this consensus dataset. The JDCBS (https://www.juvenileDermatomyositis.org.uk/) aims to incorporate this dataset as far as possible.

Research priorities defined during the consensus meeting included the need to further develop skin assessment tools that are practical within a busy clinical setting, develop an abbreviated muscle assessment tool that removes redundant items from a combined Childhood Myositis Assessment Scale and Manual Muscle Testing and to further develop PROMs so that they are applicable to JDM and acceptable to patients.

CONCLUSION

Through a robust international consensus process, a consensus dataset for JDM has been formulated that can capture disease activity and damage over time. This dataset can be incorporated into national and international collaborative research efforts, including existing clinical research databases and used routinely while evaluating patients with JDM.

Author affiliations
[1]Department of Paediatric Rheumatology, Alder Hey Children's NHS Foundation Trust, Liverpool, UK
[2]Department of Paediatric Rheumatology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
[3]Arthritis Research UK Centre for Adolescent Rheumatology, University College London, University College London Hospital, London, UK
[4]Division of Pediatric Rheumatology, IWK Health Centre and Dalhousie University, Halifax, Nova Scotia, Canada
[5]Division of Rheumatology, Università degli Studi di Genova and Istituto Giannina Gaslini Pediatria II-Reumatologia, Genoa, Italy
[6]Department of Biostatistics, MRC North West Hub for Trials Methodology Research, University of Liverpool, Liverpool, UK
[7]Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India
[8]Johns Hopkins Myositis Center, Johns Hopkins University, Baltimore, Maryland, USA
[9]2nd Department of Paediatrics, Semmelweis University, Budapest, Hungary
[10]Department of Pediatrics, The Hospital for Sick Children and University of Toronto, Toronto, Canada
[11]Department of Medicine, Rheumatology Unit, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
[12]Department of Paediatrics and Adolescent Medicine, Naestved Hospital, Region Zeeland, Naestved, Denmark
[13]Department of Dermatology, Royal Hallamshire Hospital, Sheffield, UK
[14]Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA
[15]Division of Rheumatology, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA
[16]Centre for Clinical Immunology, The Stanley Manne Children's Research Centre, Chicago, Illinois, USA
[17]Department of Paediatrics, Duke University, Durham, North Carolina, USA
[18]Environmental Autoimmunity Group, Clinical Research Branch, National Institute of Environmental Health Sciences, Bethesda, Maryland, USA
[19]Department of Paediatric Immunology and Rheumatology, Wilhelmina Children's Hospital University Medical Centre, Utrecht, The Netherlands
[20]Department of Paediatric Immunology and Rheumatology, Paediatric Hospital Dr. Juan P. Garrahan, Buenos Aires, Argentina
[21]Department of Paediatric Neurology, Alder Hey Children's NHS Foundation Trust, Liverpool, UK
[22]Infection, Immunology, and Rheumatology Section, UCL GOS Institute of Child Health, University College London, London, UK
[23]NIHR-Biomedical Research Centre at GOSH, London, UK
[24]Department of Women's and Children's Health, Institute of Translational Medicine, University of Liverpool, Liverpool, UK

Acknowledgements We would like to acknowledge the Euromyositis Research Steering Committee for their collaboration and impetus for this work, in particular Professor Ingrid Lundberg, Dr Hector Chinoy, Professor Jiri Vencovsky and Niels Steen Krogh. We acknowledge the IMACS, CARRA, PRINTO and PReS working groups for their support and collaboration. We would like to acknowledge the IMACS

membership who contributed to this work and the IMACS Scientific Committee for guidance, particularly Dr Rohit Aggarwal, Dr Frederick Miller and Dr Dana Ascherman. We would like to acknowledge the PRINTO Directors who contributed to this work and particularly acknowledge Dr Nicola Ruperto, representing PRINTO. We acknowledge the support of OMERACT and in particular, would like to thank Professor Maarten Boers for his advisory role. We would like to thank the UK Trainees Group and individuals selected by the steering committee for piloting the questionnaire before distribution. We would like to acknowledge our collaborators within the COMET group, in particular, Heather Bagley, Patient and Public Involvement Coordinator. We would also like to acknowledge the help and advice of Professor Bridget Young, Olivia Lloyd and Helen Hanson and the Clinical Studies Group consumer representatives and BSPAR Parent Group, particularly Sharon Douglas. We would like to thank young people from NIHR Young Person's Advisory Group and the JDM Young Person's Group, for their advice on patient questionnaires and information leaflets and Hema Chaplin, Patient and Public Involvement and Engagement Lead for the ARUK Centre for Adolescent Rheumatology for facilitating these groups. We acknowledge the support and collaboration of patient/parent support groups, Cure JM and Myositis UK. In particular, we would like to thank these organisations for promoting the patient and parent questionnaires via their websites/email lists. We would like to thank Katie Arnold, Lawrence Brown, Kath Forrest and Karen Barnes for their administrative support for this work. We would also like to thank Eve Smith and Nic Harman for note keeping during the consensus meeting. We would like to thank the following people for testing the dataset in practice: Bianca Lang, Silvia Rosina, Heinrike Schmeling, Krystyna Ediger, Olcay Jones, Latika Gupta, Maria Martha Katsica, Kiran Nistala, Parichat Khaosut, Ceri Turnbull, Joyce Davidson and Megan Curran.

Collaborators International Myositis Assessment and Clinical Studies group (IMACS), Paediatric Rheumatology INternational Trials Organisation (PRINTO at www.printo.it), Juvenile Dermatomyositis Research Group (JDRG) UK and Ireland, Childhood Arthritis and Rheumatology Research Alliance (CARRA), Paediatric Rheumatology European Society (PReS) JDM working group, Euromyositis Steering Committee, Core Outcome Measures in Effectiveness Trials (COMET) and Outcome Measures in Rheumatology (OMERACT) groups. A full list of contributors to the JDCBS can be found on the JDRG website (http://www.juveniledermatomyositis.org.uk).

Contributors LJM has led all parts of the study including background work, preparation of the protocol, ethics submissions, content of surveys, planning of consensus meeting, testing the dataset and writing the manuscript. CAP, AMH, AR and LRW, as members of the steering committee, have provided intellectual input and practical help into all parts of the study including background work, protocol development, Delphi survey, planning of the consensus meeting, reviewing results, refining the dataset and preparing the manuscript. AMH, AR and CAP also tested the dataset in practice. DA developed the bespoke Delphi system and provided IT support for the study including data analysis. JJK participated in the study design, was responsible for testing the Delphi system, performed the statistical analysis, helped prepare for the consensus meeting, and was involved in reviewing results and preparing the manuscript. PRW has provided expert advice on study design and Delphi methodology and analysis. AA, LC-S, TC, BMF, IL, SM, PM, RM, LMP, AMR, LGR, AvRK, RR and SS attended the consensus meeting and had intellectual input into the study. In addition, AA, AvRK, LMP, LGR and RR tested the dataset in practice. MWB has been responsible for intellectual and financial overview of the study, input into the protocol development and as a member of the steering committee has provided intellectual input into the Delphi survey and consensus meeting, reviewing results, facilitating the consensus meeting, refining the dataset and preparing the manuscript.

Funding This work was supported by Arthritis Research UK (grant number 20417); January 2014–July 2017. The UK JDM Cohort and Biomarker study has been supported by generous grants from the Wellcome Trust UK (085860), Action Medical Research UK (SP4252), The Myositis Support Group UK, Arthritis Research UK (14518), The Henry Smith Charity. LRW's work is supported in part by Great Ormond Street Children's Charity, the GOSH/ICH NIHR funded Biomedical Research Centre (BRC) and Arthritis Research UK. The JDM Cohort study is adopted onto the Comprehensive Research Network through the Medicines for Children Research Network (www.mcrn.org.uk) and is supported by the GOSH/ICH Biomedical Research Centre. LGR was supported in part by the Intramural Research Program of the National Institute of Environmental Health Sciences National Institutes of Health.

Competing interests IEL has research grants from Astra Zeneca and Bristol Myers Squibb and has served on advisory board for Bristol Myers Squibb.

Patient consent Obtained.

Ethics approval Ethical approval for the study was obtained from the IPHS Research Ethics Committee (reference IPHS-1314-321). The NHS Research Ethics Committee approved final questionnaires, consent/assent forms and patient/parent information leaflets (NRES Committee East Midlands, reference 14/EM/1259; IRAS project ID 160667).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data for this study are held securely within the University of Liverpool. There are no unpublished data openly available. A URL has been established at Liverpool University to hold the published dataset forms as described within the manuscript.

REFERENCES

1 Ravelli A, Trail L, Ferrari C, *et al*. Long-term outcome and prognostic factors of juvenile dermatomyositis: a multinational, multicenter study of 490 patients. *Arthritis Care Res* 2010;62:63–72.
2 Mathiesen PR, Zak M, Herlin T, *et al*. Clinical features and outcome in a Danish cohort of juvenile dermatomyositis patients. *Clin Exp Rheumatol* 2010;28:782–9.
3 Sanner H, Kirkhus E, Merckoll E, *et al*. Long-term muscular outcome and predisposing and prognostic factors in juvenile dermatomyositis: a case–control study. *Arthritis Care Res* 2010;62:1103–11.
4 Meyer A, Meyer N, Schaeffer M, *et al*. Incidence and prevalence of inflammatory myopathies: a systematic review. *Rheumatology* 2015;54:50–63.
5 Lundberg IE, Svensson J. Registries in idiopathic inflammatory myopathies. *Curr Opin Rheumatol* 2013;25:729–34.
6 Rider LG, Dankó K, Miller FW. Myositis registries and biorepositories: powerful tools to advance clinical, epidemiologic and pathogenic research. *Curr Opin Rheumatol* 2014;26:724–41.
7 Rider LG, Giannini EH, Harris-Love M, *et al*. Defining clinical improvement in adult and juvenile myositis. *J Rheumatol* 2003;30:603–17.
8 Rider LG, Aggarwal R, Pistorio A, *et al*. 2016 American College of Rheumatology/European League Against Rheumatism Criteria for Minimal, Moderate, and Major Clinical Response in Juvenile Dermatomyositis: an International Myositis Assessment and Clinical Studies Group/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. *Ann Rheum Dis* 2017;76:782–91.
9 National Institutes of Environmental Health and Science. International Myositis Assessment & Clinical Studies Group (IMACS). https://www.niehs.nih.gov/research/resources/imacs/index.cfm (accessed 8 Apr 2017).
10 Ruperto N, Ravelli A, Murray KJ, *et al*. Preliminary core sets of measures for disease activity and damage assessment in juvenile systemic lupus erythematosus and juvenile dermatomyositis. *Rheumatology* 2003;42:1452–9.
11 Ruperto N, Pistorio A, Ravelli A, *et al*. The Paediatric Rheumatology International Trials Organisation provisional criteria for the evaluation of response to therapy in juvenile dermatomyositis. *Arthritis Care Res* 2010;62:1533–41.
12 PRINTO. Paediatric Rheumatology INternational Trials Organization. https://www.printo.it/ (accessed 8 Apr 2017).
13 McCann LJ, Arnold K, Pilkington CA, *et al*. Developing a provisional, international minimal dataset for juvenile dermatomyositis: for use in clinical practice to inform research. *Pediatr Rheumatol Online J* 2014;12:31.
14 McCann LJ, Kirkham JJ, Wedderburn LR, *et al*. Development of an internationally agreed minimal dataset for juvenile dermatomyositis (JDM) for clinical and research use. *Trials* 2015;16:268.
15 Core Outcome Measures in Effectiveness Trials Initiative. Development of an internationally agreed minimal dataset for juvenile dermatomyositis (JDM); a rare but severe, potentially life-threatening childhood rheumatological condition. http://www.comet-initiative.org/studies/details/389?result=true (accessed 8 Apr 2017).
16 Kirkham JJ, Gorst S, Altman DG, *et al*. Core outcome set–STAndards for reporting: the COS-STAR statement. *PLoS Med* 2016;13:e1002148.
17 CARRA. Childhood Arthritis and Rheumatology Research Alliance. https://carragroup.org/ (accessed 8 Apr 2017).
18 Euromyositis. International collaboration research and treatment database for myositis specialists. https://euromyositis.eu/ (accessed 8 Apr 2017).
19 Martin N, Krol P, Smith S, *et al*. Juvenile Dermatomyositis Research Group. A national registry for juvenile dermatomyositis and other paediatric idiopathic inflammatory myopathies: 10 years' experience; the Juvenile Dermatomyositis National (UK and Ireland) Cohort Biomarker Study and Repository for Idiopathic Inflammatory Myopathies. *Rheumatology* 2011;50:137–45.
20 JDRG. Juvenile Dermatomyositis Research Group. https://www.juveniledermatomyositis.org.uk/ (accessed 8 Apr 2017).
21 PReS. Paediatric Rheumatology European Society. http://www.pres.eu/ (accessed 8 Apr 2017).
22 Rider L, Werth V, Huber A, *et al*. Measures for adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis. *Arthritis Care Red* 2013;63:118–57.

23 Varnier GC, Ferrari C, Consolaro A, *et al*. PReS-FINAL-2012: introducing a new approach to clinical care of juvenile dermatomyositis: the juvenile dermatomyositis multidimensional assessment report. *Pediatric Rheumatol* 2013;11:P25.
24 Hullmann SE, Ryan JL, Ramsey RR, *et al*. Measures of general pediatric quality of life: Child Health Questionnaire (CHQ), DISABKIDS Chronic Generic Measure (DCGM), KINDL-R, Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales, and Quality of My Life Questionnaire (QoML). *Arthritis Care Res* 2011;63:S420–30.
25 van Agt HM, Essink-Bot ML, Krabbe PF, *et al*. Test–retest reliability of health state valuations collected with the EuroQol questionnaire. *Soc Sci Med* 1994;39:1537–44.
26 Brazier J, Jones N, Kind P. Testing the validity of the Euroqol and comparing it with the SF-36 health survey questionnaire. *Qual Life Res* 1993;2:169–80.
27 Luca NJ, Feldman BM. Health outcomes of pediatric rheumatic diseases. *Best Pract Res Clin Rheumatol* 2014;28:331–50.
28 Cure JM Foundation. http://www.curejm.org/ (accessed 8 Apr 2017).
29 Myositis UK. http://www.myositis.org.uk/ (accessed 8 Apr 2017).
30 McCann LJ, Juggins AD, Maillard SM, *et al*. The Juvenile Dermatomyositis National Registry and Repository (UK and Ireland)—clinical characteristics of children recruited within the first 5 yr. *Rheumatology* 2006;45:1255–60.
31 Pilkington CA, Wedderburn LR. Paediatric idiopathic inflammatory muscle disease: recognition and management. *Drugs* 2005;65:1355–65.
32 Ramanan AV Feldman BM Clinical features and outcomes of juvenile dermatomyositis and other childhood onset myositis syndromes *Rheum Dis Clin North Am* 2002 2883357
33 Feldman BM, Rider LG, Reed AM, *et al*. Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. *Lancet* 2008;371:2201–12.
34 Shah M, Mamyrova G, Targoff IN, *et al*. The clinical phenotypes of the juvenile idiopathic inflammatory myopathies. *Medicine* 2013;92:25–41.
35 Robinson AB, Reed AM. Clinical features, pathogenesis and treatment of juvenile and adult dermatomyositis. *Nat Rev Rheumatol* 2011;7:664–75.
36 Schwartz T, Diederichsen LP, Lundberg IE, *et al*. Cardiac involvement in adult and juvenile idiopathic inflammatory myopathies. *RMD Open* 2016;2:e000291.
37 Singh S, Suri D, Aulakh R, *et al*. Mortality in children with juvenile dermatomyositis: two decades of experience from a single tertiary care centre in North India. *Clin Rheumatol* 2014;33:1675–9.
38 Huber AM, Lang B, LeBlanc CM, *et al*. Medium- and long-term functional outcomes in a multicenter cohort of children with juvenile dermatomyositis. *Arthritis Rheum* 2000;43:541–9.
39 Sanner H, Gran JT, Sjaastad I, *et al*. Cumulative organ damage and prognostic factors in juvenile dermatomyositis: a cross-sectional study median 16.8 years after symptom onset. *Rheumatology* 2009;48:1541–7.
40 Rasmussen AR, Wohlfahrt-Veje C, Tefre de Renzy-Martin K, *et al*. Validity of self-assessment of pubertal maturation. *Pediatrics* 2015;135:86–93.
41 Apaz MT, Saad-Magalhães C, Pistorio A, *et al*. Health-related quality of life of patients with juvenile dermatomyositis: results from the Pediatric Rheumatology International Trials Organisation multinational quality of life cohort study. *Arthritis Rheum* 2009;61:509–17.
42 Miller FW, Rider LG, Chung YL, *et al*. Proposed preliminary core set measures for disease outcome assessment in adult and juvenile idiopathic inflammatory myopathies. *Rheumatology* 2001;40:1262–73.
43 Feldman BM, Grundland B, McCullough L, *et al*. Distinction of quality of life, health related quality of life, and health status in children referred for rheumatologic care. *J Rheumatol* 2000;27:226–33.
44 Brown VE, Pilkington CA, Feldman BM, *et al*. An international consensus survey of the diagnostic criteria for juvenile dermatomyositis (JDM). *Rheumatology* 2006;45:990–3.
45 Brunner HI, Mina R, Pilkington C, *et al*. Preliminary criteria for global flares in childhood-onset systemic lupus erythematosus. *Arthritis Care Res* 2011;63:1213–23.
46 Ruperto N, Hanrahan LM, Alarcón GS, *et al*. International consensus for a definition of disease flare in lupus. *Lupus* 2011;20:453–62.
47 Christen-Zaech S, Seshadri R, Sundberg J, *et al*. Persistent association of nailfold capillaroscopy changes and skin involvement over thirty-six months with duration of untreated disease in patients with juvenile dermatomyositis. *Arthritis Rheum* 2008;58:571–6.
48 Schmeling H, Stephens S, Goia C, *et al*. Nailfold capillary density is importantly associated over time with muscle and skin disease activity in juvenile dermatomyositis. *Rheumatology* 2011;50:885–93.
49 Tiao J, Feng R, Berger EM, *et al*. Evaluation of the reliability of the cutaneous dermatomyositis disease area and severity index and the cutaneous assessment tool-binary method in juvenile dermatomyositis among paediatric dermatologists, rheumatologists and neurologists. *Br J Dermatol* 2017.

EXTENDED REPORT

Ideal target for psoriatic arthritis? Comparison of remission and low disease activity states in a real-life cohort

Leonieke J J van Mens,[1] Marleen G H van de Sande,[1] Arno W R van Kuijk,[2] Dominique Baeten,[1] Laura C Coates[3]

Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-211998).

[1]Clinical Immunology & Rheumatology, Amsterdam Rheumatology and Immunology Center, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands
[2]Department of Rheumatology, Amsterdam Rheumatology and Immunology Center, Amsterdam, The Netherlands
[3]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

Correspondence to
Dr Laura C Coates, Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, Botnar Research CentreWindmill Road, Oxford, OX3 7LD, UK;
laura.coates@ndorms.ox.ac.uk

Received 29 June 2017
Revised 1 September 2017
Accepted 6 October 2017
Published Online First
28 October 2017

To cite: van Mens LJJ, van de Sande MGH, van Kuijk AWR, *et al*. *Ann Rheum Dis* 2018;**77**:251–257.

ABSTRACT

Background Psoriatic arthritis (PsA) recommendations state that the target of treatment should be remission or low disease activity (LDA). We used a real-life dataset to compare different potential targets.

Methods 250 patients with PsA considered in an acceptable disease state according to their rheumatologist were included. Targets for remission were the Disease Activity Index for Psoriatic Arthritis (DAPSA) and clinical DAPSA (cDAPSA) remission (≤4), very low disease activity (VLDA) and Psoriatic Arthritis Disease Activity Score ≤1.9. LDA targets analysed were the DAPSA ≤14, cDAPSA ≤13, minimal disease activity (MDA) and adjusted MDA targets: MDAjoints with both tender joint count (TJC) and swollen joint count (SJC) mandated, MDAskin (psoriasis area and severity index (PASI) mandated) and MDAjoints&skin with TJC, SJC and PASI mandated.

Results Comparison of the several candidate targets demonstrates that VLDA is achieved by the lowest proportion of patients and includes patients with the lowest residual disease activity compared with the other remission targets. The modified MDA measures are the most stringent targets for LDA in terms of residual disease on joints, psoriasis and enthesitis within patients achieving the target. In both remission and LDA, the inclusion of C reactive protein did not show an added value. The exclusion of a skin domain, as in the DAPSA measures, resulted in negligence of skin disease and a negative impact on the quality of life in some patients.

Conclusions The different remission and LDA targets show us significant overlap between measures, but these measures targeting the same definition do differ in terms of allowance of residual disease. Inclusion of laboratory markers seems unnecessary, although exclusion of a skin domain may result in psoriasis not being assessed resulting in residual impactful skin disease.

INTRODUCTION

Treatment guidelines for psoriatic arthritis (PsA) by European League Against Rheumatism and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommend to aim for remission or the lowest possible disease activity in all involved domains of the disease.[1 2] Clinical remission in psoriatic arthritis is mostly defined as a complete absence of disease activity, with no signs or symptoms of in all domains of the disease.[3] However, the specific target to define remission or low disease activity is not specified further by the treatment recommendations.

It is still under debate what the target to measure the disease state should be. Several composite scores are developed specifically for PsA, most focusing on multiple domains considered important to assess: (1) the minimal disease activity (MDA), which is a seven-component score including skin, enthesitis, tender and swollen joint counts (SJCs) and patient reported domains including pain and global disease activity score as well as the Health Assessment Questionnaire (HAQ),[4 5] (2) the Psoriatic Arthritis Disease Activity Score (PASDAS), which includes SJW, enthesitis, dactylitis, skin, C reactive protein (CRP), patient-reported and physician-reported global disease activity and the short form 36 questionnaire (SF-36) questionnaire on physical functioning[6] and (3) the Disease Activity Index for Psoriatic Arthritis (DAPSA), which focuses on peripheral arthritis and includes tender and SJCs, CRP and patient-reported pain and global disease activity scoring adjusted later to exclude the CRP, the clinical DAPSA (cDAPSA).[7]

All three measures can be used to define remission or low disease state. For MDA, a modified version was developed to use as a remission target, the very low disease activity (VLDA).[8] Furthermore, adjusted versions of the MDA, with a focus on joint and skin symptoms, were developed. Specific cut-off values to define remission or low disease activity were developed for (c)DAPSA, as well as a cut-off for near remission in PASDAS.[9 10] However, little data are published on comparing these measures, and it is unknown if these measures reflect the same clinical disease activity on the various disease domains. We have previously set up a cohort of patients with psoriatic arthritis focusing on a quiescent disease state.[11] As the disease targets will be a complimentary tool in clinical practice, this cohort is an ideal group of patients to assess their performance in.

In the present study, we aimed to compare these composite scores proposed as a target for remission or low disease activity in PsA using an existing real-life data set of PsA patients with quiescent disease according to their rheumatologist. We investigated which patients fulfil definitions of these criteria, how much overlap there is in fulfilling the different targets and how much residual disease in the various domains is present in the different composite scores.

METHODS

An existing dataset was used: data from a cross-sectional study of 250 PsA patients with quiescent disease according to the treating rheumatologist was used and recruited from routine clinical visits. Patients had to have been on stable treatment for at least 6 months, regardless of therapy. Mean age 55 years, two-thirds of the patients were male, mean disease duration was 12.7 (9.2) years, age at arthritis onset was 42.7 (12.3) years. On group level, disease activity was low, with a mean swollen joint count (SJC) of (median(IQR)) 0 (0–1), tender joint count of 1 (0–5), psoriasis area and severity index (PASI) score of 0.3 (0–1.5), enthesitis present in 17 of 250 patients and dactylitis in 2 of 250 patients. The patients' characteristics are shown in more detail in see online supplementary file 1.[11]

Four potential definitions of remission/inactive disease were used where all items required for the definitions were available in this dataset:

1. VLDA where all seven of the MDA cut points are met: tender joint count (TJC) ≤1; SJC ≤1; enthesitis count ≤1; PASI ≤1; patient global visual analogue scale (VASptGlobal) ≤20 mm; patient pain (VASptPain) ≤15 mm; and HAQ ≤0.5.
2. DAPSA remission[4] where DAPSA ≤4: TJC+SJC+VASpt-Global (cm)+VASptPain (cm)+CRP (mg/L).
3. cDAPSA remission where cDAPSA ≤4: TJC+SJC+VASpt-Global (cm)+VASptPain (cm).
4. Near remission in the psoriatic arthritis disease activity score (PASDAS) where PASDAS ≤1.9.

Six potential definitions for low or minimal disease activity were used:

1. DAPSA low disease (DAPSA=TJC+SJC+bal+VASptPain +CRP) ≤14.
2. cDAPSA low disease (DAPSA=TJC+SJC+VASpt-Global+ VASptPain) ≤13.
3. MDA 5/7 where any five of the seven cut points are required to be met.
4. MDA joints where both the tender and swollen joint count cut points are required to be met with any 3/5 of the remaining cut points (enthesitis, skin, VASptGlobal, VASpt-Pain and HAQ).
5. MDA skin where skin is required plus 4/6 remaining cut points (TJC, SJC, enthesitis, VASptGlobal, VASptPain and HAQ).
6. MDA joints and skin where the TJC, SJC and skin cut points are required to be met with any 2/4 of the remaining cut points (enthesitis, VASptGlobal, VASptPain and HAQ).

Proportions achieving each criteria were calculated. The agreement between the tested definitions was established using 2×2 tables and percentage exact agreement (PEA) and calculation of a kappa. The proportion of residual disease was established for key clinical domains of PsA (peripheral arthritis, enthesitis, psoriasis and dactylitis) and levels of systemic inflammation, as measured by CRP, were assessed.

RESULTS

Comparisons of the measures for remission/inactive disease

Of the total population (250 patients), 107 (43.7%) fulfilled DAPSA remission, 113 (45.7%) were in cDAPSA remission, 56 (22.5%) met VLDA and 37 (19.5%) were in PASDAS near remission. The DAPSA could not be calculated in 4/250 patients due to missing CRP values; 1/250 patients had incomplete data to calculate the VLDA (missing PASI score), the PASDAS score could not be calculated in 23/250 patients due to missing SF36 scores and the majority of these patients did not fulfil any of the remission targets (18/23). There was a very high agreement between DAPSA and cDAPSA remission (kappa 0.959) reflecting the similarity of the two definitions (the inclusion of CRP is different). The agreement between both DAPSA/cDAPSA and VLDA was moderate (kappa of 0.516 and 0.544, respectively). The agreement between VLDA/cDAPSA/DAPSA and PASDAS is considered fair, with a kappa of 0.403, 0.321, 0.319, respectively (table 1A).

Table 1 Kappa scores

(A) **Kappa scores of remission/inactive disease and low disease activity measures**

	PASDAS	VLDA	cDAPSA	DAPSA
PASDAS	X	0403	0321	0319
VLDA	0.403	X	0516	0544
cDAPSA	0321	0516	X	0959
DAPSA	0319	0544	0959	X

(B) **Kappa scores of low disease activity measures**

	MDA	MDA skin	MDA joints	MDA skin&joints	cDAPSA LDA	DAPSA LDA
MDA	X	0668	0647	0425	0611	0596
MDA skin	0668	X	0431	0700	0356	0343
MDA joints	0647	0431	X	0722	0372	0360
MDA joints&skin	0425	0700	0722	X	0227	0218
cDAPSA_LDA	0611	0356	0372	0227	X	0988
DAPSA LDA	0596	0343	0360	0218	0988	x

cDAPSA, clinical DAPSA; DAPSA, Disease Activity Index for Psoriatic Arthritis; LDA, low disease activity; MDA, minimal disease activity; PASDAS, Psoriatic Arthritis Disease Activity Score; VLDA, very low disease activity

The concordance in fulfilment of the criteria is presented in figure 1. VLDA and PASDAS are the most stringent, and the DAPSA scores the least. All patients who met VLDA were in DAPSA/cDAPSA remission. Of those patients in DAPSA remission but not in VLDA, 43/56 patients did not fulfil 1/7 domains, while nine did not fulfil 2/7 domains. Domains not fulfilled were skin (n=33), tender joints (n=7), swollen joints (n=1), enthesitis (n=3), VAS scores (n=6) or HAQ (n=9). In the nine patients who did not achieve VLDA due to a high HAQ score, eight of them met the MDA criteria suggesting that they would have fulfilled an alternative LDA target. In 4/9, the HAQ domain was the only criteria that was not met; in 5/9, there were other

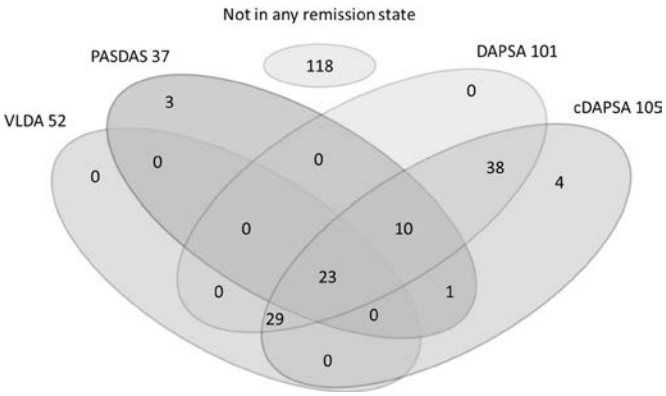


Figure 1 Venn diagram representing the number of patients meeting different remission criteria. The graph only includes those patients where all criteria were available (n=226). cDAPSA, clinical DAPSA; DAPSA, Disease Activity Index for Psoriatic Arthritis; PASDAS, Psoriatic Arthritis Disease Activity Score; VLDA, very low disease activity.

Table 2 Residual disease activity in different measures for remission

		cDAPSA remission (total 113)	DAPSA remission (total 107)	VLDA (total 56)	PASDAS <1.9 (n=37)
PASDAS	**Mean (SD)**	**2.16 (0.52)**	**2.13 (0.49)**	**1.97 (0.42)**	**1.6 (0.20)**
Swollen joint count n (%)	0	101 (89)	96 (90)	53 (95)	33 (89)
	1–3	12 (11)	11 (10)	3 (5)	4 (11)
	4–6	0 (–)	0 (–)	0 (–)	0 (–)
Tender joint count n (%)	0	93 (82)	89 (83)	51 (91)	28 (76)
	1–3	20 (18)	18 (17)	5 (9)	6 (16)
	4–7	0 (–)	0 (–)	0 (–)	2 (8)
	8+	0 (–)	0 (–)	0 (–)	0 (–)
Leeds enthesitis index n (%)	0	108 (96)	102 (96)	56 (100)	37 (100)
	1–2	4 (–)	4 (–)	0 (–)	0 (–)
	4	1 (–)	1 (–)	0 (–)	0 (–)
Dactylitis count n (%)	0	113 (100)	107 (100)	56 (100)	37 (100)
PASI n (%)	0–1	79 (70)	74 (69)	56 (100)	32 (86)
	>1	34 (30)	33 (31)	0 (–)	5 (14)
CRP >normal value (5 mg/L) n (%)		11 (10)	8 (7.5)	5 (9)	1 (3)

cDAPSA, clinical DAPSA; CRP, C reactive protein; DAPSA, Disease Activity Index for Psoriatic Arthritis; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI, psoriasis area and severity index; VLDA, very low disease activity.

residual domains (PASI n=2, enthesitis score n=2 and VASglobal n=2).

Residual disease activity in patients fulfilling the remission/inactive disease measures

Levels of residual disease activity in patients meeting the different measures for remission/inactive disease are shown in table 2 and figure 2.

These measures do not represent similar numbers of residual disease in all domains. The presence of swollen joints and active enthesitis was similar across the different measures (SJC ≥1 in 5%–10% of patients and enthesitis ≥1 in 4%–0% of patients). TJCs were lower in VLDA (TJC ≥1 in 9%) and higher in the DAPSA, cDAPSA and PASDAS remission groups (TJC ≥1 in 17%, 18% and 25%, respectively). Skin disease was more prevalent in both DAPSA measures (a PASI ≥1 in resp. 30% of cDAPSA and 31% of patients with patients) in contrast with 14% in the PASDAS patients and 0% in VLDA. cDAPSA and VLDA had similar proportions of patients with raised CRP (10% and 9%) in comparison with DAPSA and PASDAS (8%), although CRP is not assessed in either cDAPSA or VLDA definitions.

VLDA presents as a more stringent cut-off with the least residual disease in PASI and tender joint count. PASDAS seems to include more patients with tender joints but less with an elevated CRP and less patients with active skin disease in comparison with the other measures. Both DAPSA scores considered more patients in remission but did allow for more residual disease activity in the domains tender joints, skin disease and enthesitis in comparison with the other measures.

Residual disease activity in remission measures related to quality of life (QoL)

In those patients with a raised CRP, no differences were found on patient reported outcomes (PROs) on QoL and functionality. Very few patients had residual enthesitis in any definition and those in remission with an enthesitis did not report significantly worse functioning or QoL, although some of the BASDAI scores were higher. Residual skin disease did affect DLQI, although not to a very high extent. For patients with 'active' skin disease (with PASI scores ≥1), no effect is seen on all quality-adjusted life year measures and the 74/110 patients fulfilling DAPSA with a PASI of ≥1 do not present with a higher score on the DLQI scale. The group with a PASI of >2 (present in 20/110 pts achieving DAPSA remission) was reflected by an impact on DLQI (2.85 (SD 2.9) vs 1 (2.3) p=0.003). No conclusions can be drawn on the effects of residual dactylitis as this cohort presented with a very low amount of patients with an active dactylitis during the trial visit.

Low disease activity and inactive disease measures

Comparisons of the low disease activity/inactive disease measures

Of the total population, 162 (65%) achieved MDA, 113 (45.6%) achieved MDAjoints, 114 (46%) achieved MDAskin, 79 (31.6%) achieved MDAjoints&skin, 195 (78%) achieved DAPSA LDA, 195 (78%) achieved cDAPSA LDA.

The concordance in fulfilment of the criteria is presented in figure 3.

A high agreement is seen between the DAPSA/cDAPSA and the MDA5/7 (kappa of 0596 and 0611, respectively) table 1B. Agreement between the DAPSA and the alternative MDA measures (MDAjoints, MDAskin and MDAjoints&skin) is lower as these targets are more stringent.

Residual disease activity in patients fulfilling low disease activity/inactive disease measures

Levels of residual disease activity in patients meeting low disease activity/MDA/new MDA measures are shown in table 3 and figure 3.

Higher levels of tender and swollen joint counts and skin disease are seen in the DAPSA LDA measures in comparison with all four MDA scores. By their definition, MDAjoints and MDAjoints&skin show an even stricter cut-off on joint involvement, with a single swollen joint in only 10% and 5%, respectively, and a tender joint in only 14% and 2% of the patients.

Between the different outcome measures, the presence of patients with a raised CRP is similar (approximately 12% in all measures).

Residual disease activity in remission measures related to QoL

Not including an enthesitis measure in the score does not seem to make much difference; it does not result in a group of patients with active disease and a high disease burden, as only five patients with an active enthesitis fulfil (DAPSA) LDA criteria, these patients did not differ in QoL scores in comparison with other DAPSA LDA patients. No differences were found on PROs on QoL and functionality between patients with and without a raised CRP. A PASI score >1 was more prevalent in the DAPSA cut-off groups in comparison with the MDA/new MDA measures (46% in DAPSA LDA n and between 0% and29% in the different MDA measures). The patients with active psoriasis in the DAPSA LDA group did report significantly larger impact of skin disease on dermatology related QoL (DLQI scale) (PASI 0–1: 1 to 25 (SD2,4) vs PASI >1: 1.55 (SD2.7), p=0024.

DISCUSSION

The analysis of different remission and low disease activity targets in this real life clinical cohort do show significant overlap

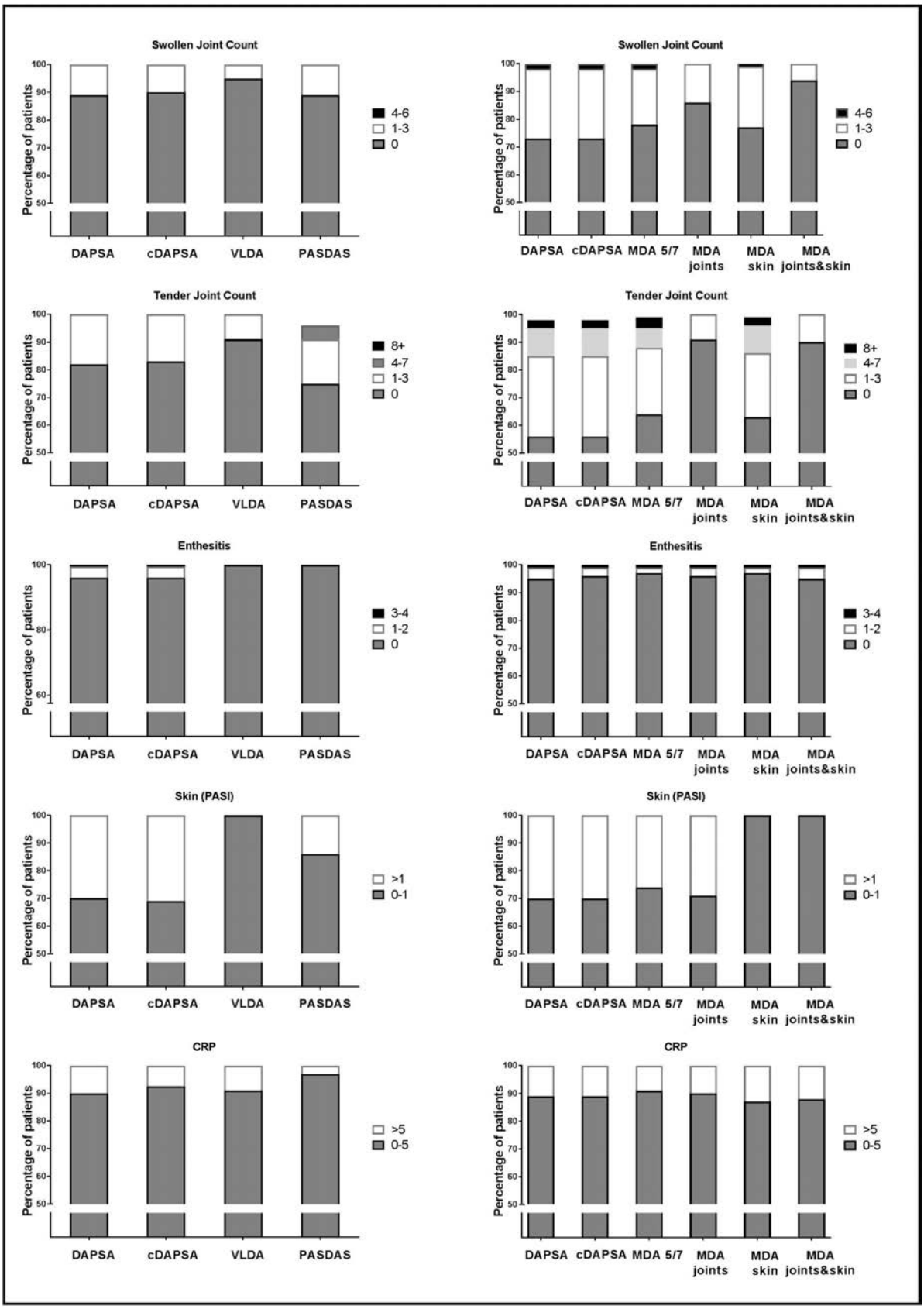


Figure 2 The remaining residual disease activity in different disease domains within the subgroups of patients meeting the different remission criteria. The graphs show residual disease on different disease activity measures (top to bottom: swollen joints, tender joints, enthesitis, skin and CRP) in the patient groups fulfilling the different remission measure (left graphs) or LDA measure (right graphs). Stacked bars divide the patients fulfilling each remission/LDA measure in groups according to the amount of residual disease present. cDAPSA, clinical DAPSA; CRP, C reactive protein; DAPSA, Disease Activity Index for Psoriatic Arthritis; LDA, low disease activity; MDA, minimal disease activity; PASDAS, Psoriatic Arthritis Disease Activity Score; VLDA, very low disease activity.

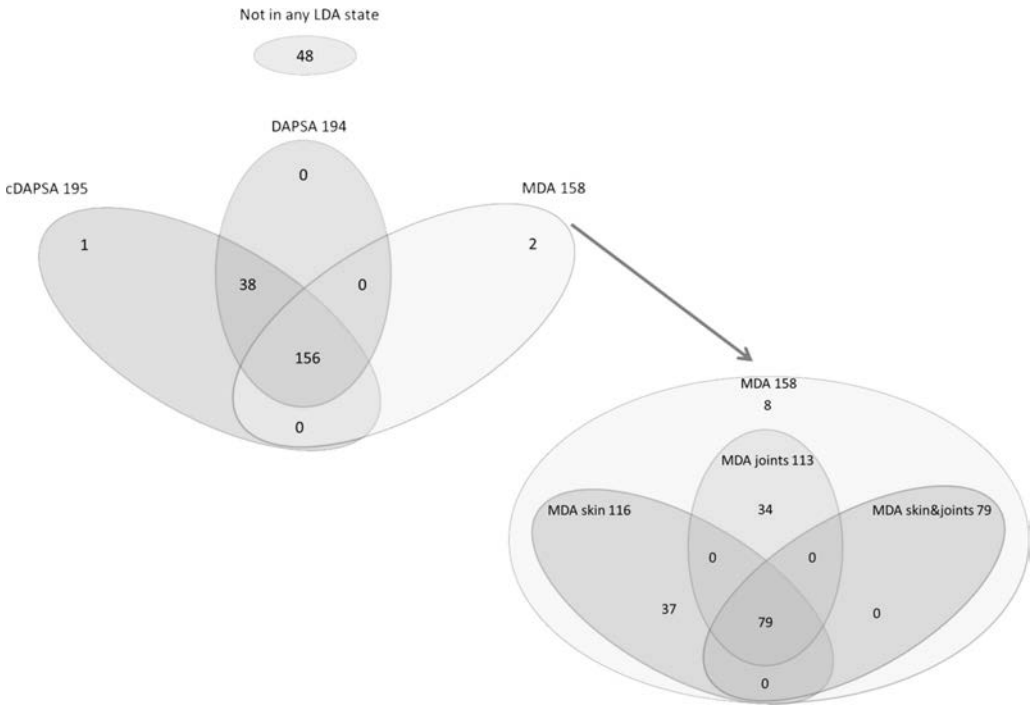


Figure 3 Venn diagram representing the number of patients meeting different low disease activity criteria. The graphs only include those patients where all criteria were available (n=245). cDAPSA, clinical DAPSA; DAPSA, Disease Activity Index for Psoriatic Arthritis; LDA, low disease activity; MDA, minimal disease activity.

between the measures. However, it is clear that these different measures targeting the same conceptual definition (ie, remission or low disease activity) do result in different levels of residual disease present in individuals. Comparison of the several candidate measures demonstrates that VLDA is achieved by the lowest proportion of patients in this cohort. This suggests that it may be the most stringent target for remission of inactive disease, although it could be difficult to attain and may be more stringent than patient and physician opinion of acceptable disease states. The modified MDA measures are the most stringent targets for low disease activity in terms of residual disease on joints, psoriasis and enthesitis within patients achieving the target. In both remission and LDA measures the addition of CRP did not show an added value. The exclusion of a domain for psoriasis, as in the DAPSA measures, resulted in negligence of skin disease and a negative impact on the QoL in some patients.

For this study, we used three different measure concepts validated for psoriatic arthritis, the MDA and the adjusted versions (MDAskin/MDAjoints and MDAjoints&skin as well as VLDA), DAPSA and PASDAS. The MDA and adjusted MDA measures all use a modular approach where an individual cut-off for each domain is specified and depending on the measure used, a number of cut-offs need to be met. In contrast, the DAPSA and PASDAS measures sum the scores of the individual components into one final number. In both the DAPSA and PASDAS measures for remission and low disease activity, higher levels

Table 3 Residual disease activity in different measures for low disease activity

		DAPSA LDA (195)	cDAPSA LDA (195)	MDA5/7 (162)	MDA joints (117)	MDA skin (120)	MDA skin & joints (83)
PASDAS	**Mean (SD)**	**2.49 (0.66)**	**2.48 (0.66)**	**2.3 (0.6)**	**2.26 (0.60)**	**2.29 (0.59)**	**2.2 (0.63)**
Swollen joint count n (%)	0	143 (74)	143 (73)	126 (78)	101 (86)	92 (77)	78 (94)
	1–3	48 (25)	48 (25)	33 (20)	16 (14)	26 (22)	5 (6)
	4–6	4 (2)	4 (2)	3 (2)	0 (0)	2 (2)	0 (0)
Tender joint count n (%)	0	110 (56)	111 (56)	103 (64)	106 (91)	76 (63)	75 (90)
	1–3	56 (29)	56 (29)	39 (24)	11 (9)	28 (23)	8 (10)
	4–7	19 (10)	19 (10)	12 (7)	0 (0)	12 (10)	0 (0)
	8+	6 (3)	5 (3)	6 (4)	0 (0)	4 (3)	0 (0)
Enthesitis count n (%)	0	186 (95)	187 (96)	157 (97)	112 (96)	116 (97)	79 (95)
	1–2	7 (4)	6 (3)	4 (2)	4 (3)	3 (2)	3 (4)
	3–4	2 (1)	2 (1)	1 (1)	1 (1)	1 (1)	1 (1)
Dactylitis count n (%)	0	195 (100)	195 (100)	162 (100)	117 (100)	120 (100)	83 (100)
PASI n (%)	0–1	136 (70)	136 (70)	120 (74)	83 (71)	120 (100)	83 (100)
	>1	59 (30)	59 (30)	42 (26)	34 (29)	0 (0)	0 (0)
CRP (normal <5 mg/dL) n (%)	Raised	22 (11)	22 (11)	18 (11)	12 (10)	15 (13)	10 (12)

cDAPSA, clinical DAPSA; CRP, C reactive protein; DAPSA, Disease Activity Index for Psoriatic Arthritis; LDA, low disease activity; MDA, minimal disease activity.

of residual musculoskeletal disease were seen in comparison with the VLDA and the MDAskin/joint measures. An active domain can be hidden when other domains are relatively unaffected, resulting in the inclusion of patients with active disease within the group of patients seen as in remission or low disease activity state.

The DAPSA focuses specifically on peripheral joint disease, and some argue that this is ideal as it can reflect change accurately in this single domain. However, because it does not measure other domains of the disease, active disease in these domains is missed. Residual skin disease was highest in patients achieving DAPSA or cDAPSA remission when compared with the other remission targets as well as for the DAPSA and cDAPSA low disease cut-offs in comparison with the adjusted MDA measures. Within our group of patients, this resulted in a group of patients, seen as in a low disease activity state, with remaining skin disease impacting their QoL. This analysis highlights the need for multiple separate measures for different domains to be assessed if a multidimensional definition is not used to ensure that remission retains face validity for the patients.

The MDA domains include a measure of function as they were taken from the core domain of PsA and are in line with similar definitions in RA.[12 13] Concern has been raised that, as the HAQ will be affected by non-reversible damage as well as disease activity, this may limit their applicability.[14] In this cohort with established disease (mean disease duration of 12.7 years), very few patients failed to achieve VLDA due to HAQ alone, but they did achieve MDA and its more stringent variations. Another concern that has been raised is the influence of comorbid fibromyalgia on the outcome measures and potential targets. Brikman *et al* have shown that fibromyalgia impacts on both DAPSA, MDA and other scores. Unfortunately, we do not have fibromyalgia data on these patients but given that the items within the targets overlap significantly, we do not anticipate a differential effect of fibromyalgia between the different measures.[15]

Not all measures used in this comparison included an inflammatory marker. The DAPSA and PASDAS include a CRP, and cDAPSA and MDA measures do not. These data suggest that the inclusion of CRP is unnecessary to include as a similar proportion of patients have a raised CRP in all definitions. Those patients with a raised CRP that fulfilled the disease targets did not show a difference in other disease activity measures or on PRO scores. A target without an inflammatory marker will be more practical in clinical practice and if routine laboratory assessment is not needed for other reasons a lower burden for the patient as well.

Another important factor worth considering when choosing a tool for clinical practice is the feasibility and practicality of the tool. The tool should ideally be easy to calculate, as limited time during daily practice makes a simple to obtain target easier to incorporate in clinical practice. Second, when many different outcomes need to be assessed, it will be laborious to calculate these individual scores and the chance increases that information is missing. Third, the transparency and presentation of the tool after calculation is of importance as the individual components will still remain important to consider when targeting a therapy.

Several considerations can be made to the assessed measures in this study, all having their own strengths and weaknesses: the DAPSA focuses only on peripheral joint disease and does not include a skin or enthesitis component; the PASDAS is less transparent on individual components, and the complexity makes it more time consuming to calculate this measure; the MDA is a binary measure (and not a continuous one), therefore scores do not show an increase in disease activity after the bar for remission or LDA is achieved.

It is important to note that we made no attempt to perform new psychometric analyses on measures and only restricted our work to answer the question how the available, validated measures perform and compare with one each other. With the ongoing efforts on gaining consensus on a target for the treatment of PsA, more information on the impact of residual disease is needed. The cut-off for acceptable disease activity is of importance as with a stricter target more intensive treatments might be started, might lead to a more intensive treatment, and this eventually could result in overtreatment of patients with consequences in terms of side effects and an increase in costs. The ideal stringency of a target with assessment of residual disease in the various clinical domains of PsA should be a focus of future research. An observational study shows lower levels of disease activity in remission versus LDA states and better QoL.[16] It remains unknown whether meeting a strict target such as VLDA is superior in reducing impact on patient outcomes such as QoL, radiographic progression and functioning, in comparison with less stringent targets. Ideally a trial comparing remission and low disease activity, incorporating efficacy, safety, cost–benefit and patient opinion is needed.

Contributors All authors fulfilled the ICMJE recommendations for authorship, were involved in drafting and reviewing of the manuscript and approved the final version.

Funding The original cohort was supported by an unrestricted grant from Pfizer B.V.

Competing interests LJvM, none declared. MGHvdS has received speakers/consultancy fees from Takeda, Tillotts and Benecke MSD. DB has received research grants and speakers/consultancy fees from Pfizer, MSD, AbbVie, UCB, Novartis, Janssen, Boehringer Ingelheim; speakers/consultancy fees from Eli Lilly, Roche, BMS and Glenmark; and is currently an employee of UCB. AWRvK has received speakers/consultancy fees from Celgene, Janssen-Cilag, Novartis, MSD and Roche. LCC, none declared.

Patient consent Obtained.

Ethics approval METC AMC Amsterdam.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Coates LC, Kavanaugh A, Mease PJ, *et al*. Group for research and assessment of psoriasis and psoriatic arthritis: Treatment recommendations for psoriatic arthritis 2015. *Arthritis Rheumatol* 2016;67.
2 Gossec L, Smolen JS, Ramiro S, *et al*. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis* 2016;75:499–510.
3 Kavanaugh A, Fransen J. Defining remission in psoriatic arthritis. *Clin Exp Rheumatol* 2006;24:S-83-7.
4 Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. *Arthritis Care Res* 2010;62:965–9.
5 Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis* 2010;69:48–53.
6 Helliwell PS, FitzGerald O, Fransen J, *et al*. The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). *Ann Rheum Dis* 2013;72:986–91.
7 Smolen JS, Schoels M, Aletaha D, *et al*. Disease activity and response assessment in psoriatic arthritis using the Disease Activity index for PSoriatic Arthritis (DAPSA). A brief review. *Clin Exp Rheumatol* 2015;33:48–50.
8 Coates LC, Helliwell PS. Defining low disease activity states in psoriatic arthritis using novel composite disease instruments. *J Rheumatol* 2016.
9 Schoels MM, Aletaha D, Alasti F, *et al*. Disease activity in psoriatic arthritis (PsA): defining remission and treatment success using the DAPSA score. *Ann Rheum Dis* 2016;75:811–8.
10 Helliwell PS, FitzGerald O, Fransen J. Composite disease activity and responder indices for psoriatic arthritis: a report from the GRAPPA 2013 meeting on development of cutoffs for both disease activity states and response. *J Rheumatol* 2014;41:1212–7.

11 van Mens LJJ, Turina MC, van de Sande MGH, *et al*. Residual disease activity in psoriatic arthritis: discordance between the rheumatologist's opinion and minimal disease activity measurement. *Rheumatology* 2017:1–8.
12 Gladman DD, Mease PJ, Strand V, *et al*. Consensus on a core set of domains for psoriatic arthritis. *J Rheumatol* 2007;34:1167–70.
13 Wells GA, Boers M, Shea B, *et al*. Minimal disease activity for rheumatoid arthritis: a preliminary definition. *J Rheumatol* 2005;32:2016–24 http://www.jrheum.org/content/32/10/2016.
14 Husted JA, Gladman DD, Farewell VT, *et al*. Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. *Arthritis Rheum* 2001;45:151–8.
15 Brikman S, Furer V, Wollman J, *et al*. The effect of the presence of fibromyalgia on common clinical disease activity indices in patients with psoriatic arthritis: A Cross-sectional Study. *J Rheumatol* 2016;43:1749–54.
16 Queiro R, Crespillo JC, Montilla C, *et al*. [Abstract] Very lowdisease activity and impact of disease in a Spanish population with psoriatic arthritis. *Ann Rheum Dis* 2017.

OPEN ACCESS

EXTENDED REPORT

Development and psychometric validation of a patient-reported outcome measure to assess fears in rheumatoid arthritis and axial spondyloarthritis: the Fear Assessment in Inflammatory Rheumatic diseases (FAIR) questionnaire

Laure Gossec,[1,2] Pierre Chauvin,[3] Alain Saraux,[4,5] Christophe Hudry,[6] Gabrielle Cukierman,[7] Thibault de Chalus,[7] Caroline Dreuillet,[8] Vincent Saulot,[8] Sabine Tong,[9] Françoise Russo-Marie,[8] Jean-Michel Joubert,[7] Francis Berenbaum[10,11]

Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-212000).

For numbered affiliations see end of article.

Correspondence to
Professor Laure Gossec, Service de rhumatologie, Hôpital Pitié Salpêtrière, AP-HP, Paris, France; laure.gossec@aphp.fr

Received 29 June 2017
Revised 15 September 2017
Accepted 6 October 2017
Published Online First
4 November 2017

ABSTRACT

Objectives To develop and validate an outcome measure for assessing fears in patients with rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA).

Methods Fears were identified in a qualitative study, and reformulated as assertions with which participants could rate their agreement (on a 0–10 numeric rating scale). A cross-sectional validation study was performed including patients diagnosed with RA or axSpA. Redundant items (correlation >0.65) were excluded. Internal consistency (Cronbach's α) and factorial structure (principal component analysis) were assessed. Patients were classified into fear levels (cluster analysis). Associations between patient variables and fear levels were evaluated using multiple logistic regression.

Results 672 patients were included in the validation study (432 RA, 240 axSpA); most had moderate disease activity and were prescribed biologics. The final questionnaire included 10 questions with high internal consistency (α: 0.89) and a single dimension. Mean scores (±SD) were 51.2 (±25.4) in RA and 60.5 (±22.9) in axSpA. Groups of patients with high (17.2%), moderate (41.1%) and low (41.7%) fear scores were identified. High fear scores were associated with high Arthritis Helplessness Index scores (OR 6.85, 95% CI (3.95 to 11.87)); high Hospital Anxiety and Depression Scale anxiety (OR 5.80, 95% CI (1.19 to 4.22)) and depression (OR 2.37, 95% CI (1.29 to 4.37)) scores; low education level (OR 3.48, 95% CI (1.37 to 8.83)); and high perceived disease activity (OR 2.36, 95% CI (1.10 to 5.04)).

Conclusions Overall, 17.2% of patients had high fear scores, although disease was often well controlled. High fear scores were associated with psychological distress. This questionnaire could be useful both in routine practice and clinical trials.

To cite: Gossec L, Chauvin P, Saraux A, *et al*. *Ann Rheum Dis* 2018;**77**:258–263.

INTRODUCTION

Chronic inflammatory rheumatic diseases (CIRDs) such as rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA) have a major impact on quality of life.[1] They interfere with many aspects of daily functioning, including recreational activities, work, family life and relationships.[2] These aspects of disease burden are frequently underestimated or unrecognised by the patient's family and friends, as well as the treating physician.[2 3] In addition, these diseases may be associated with considerable psychological distress, including anxiety or depression.[4–6] Several studies, including a recent qualitative study in France,[7] have shown that patients with CIRDs have specific fears about how their disease will progress, limitations in daily activities, being a burden on others and treatment.[2 7–9] Although these aspects are important to patients, they are currently difficult to assess due to the lack of a specific evaluation tool.

Although several patient-reported outcome (PRO) measures assess emotional status or anxiety levels,[10–13] many of these are generic and none, to our knowledge, specifically assess fears.[14] A questionnaire focusing on CIRD-related fears would potentially be useful both in the context of everyday care (eg, to help understand patients' motivations and reluctance towards treatments) and in clinical trials, since such fears may have an impact on the efficacy of a study drug.[15] Current recommendations on PRO development and validation include grounding PROs in the patient perspective, and performing adequate psychometric validation of all such measures.[16–20]

The objectives of the present study were to develop a PRO for fear assessment in patients with RA or axSpA, and to perform a preliminary psychometric validation of the resulting instrument.

METHODS

This study was part of a larger programme of research on patient perceptions in chronic progressive rheumatic diseases. The programme was supervised by a steering committee (the authors of this manuscript), composed of rheumatologists, psychologists, methodologists and representatives of the scientific staff of the Arthritis Fondation Courtin and of UCB Pharma, who jointly funded the programme.

Development of a preliminary questionnaire

In a previously published qualitative study,[7] 25 patients with RA and 25 with axSpA participated

in semistructured interviews about their perceptions of the diseases. Interviews were transcribed verbatim, and the data extracted inductively from the interview transcripts. Fears about the future course of the disease, the impact of disease and its treatment were frequently expressed, and appeared to be shared in common between patients with axSpA and those with RA.

In the present study, all fears that were expressed by >5% of patients in the qualitative study were used. Non-redundant statements were then rephrased as assertions over two working sessions involving members of the Steering Committee and a patient research partner (a member of the EULAR PARE (People with Arthritis and Rheumatism) programme). The agreement with each item was assessed on a scale of 0–10 ('totally disagree' to 'totally agree'). The questions were then tested in a sample of 10 patients with RA and 10 with axSpA for linguistic validation, and cognitive debriefing was performed during individual face-to-face interviews with trained interviewers. This preliminary questionnaire contained 23 items related to fears.

Validation study

This was a prospective, cross-sectional study in patients with RA or axSpA in France. Participants were recruited by hospital and community rheumatologists between July 2014 and October 2015.

Participants

All rheumatologists currently practising in France were invited to participate in the study through post and email. Each participating rheumatologist was expected to invite up to 20 consecutive patients with RA or axSpA attending a routine consultation who were aged >18 years, and had a diagnosis of RA according to the ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) classification criteria,[21] or of axSpA according to the ASAS (Assessment in Spondyloarthritis International Society) classification criteria.[22] Patients with psoriatic arthritis or other CIRDs, and those who were unable to complete a questionnaire, were excluded.

Data collection

Patients were asked to complete the preliminary questionnaire, as well as the patient global assessment of overall disease activity (scored from 0 to 10), the Hospital Anxiety and Depression Scale (HADS),[11] the Arthritis Helplessness Index (AHI)[23] and, for patients with axSpA, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).[24] The patient also provided information on sociodemographic indicators, health insurance coverage, disease duration and family history of rheumatic disease. In parallel, the rheumatologist provided information on the patient's disease activity, as measured by the 28-item Disease Activity Score calculated with erythrocyte sedimentation rate (DAS28(ESR))[25] for RA, and an overall assessment of disease activity scored from 0 to 10. Information on current treatment was also collected.

In order to assess the reproducibility of the questionnaire, 30 randomly selected patients were provided with two questionnaires and invited to complete and return the second one 2 weeks later.

Finalisation and psychometric validation of the Fear Assessment in Inflammatory Rheumatic diseases questionnaire

Finalising the questionnaire

The number of items on the fear dimensions was reduced to avoid redundancy. Interitem Pearson's correlation coefficients between each pair of items were determined across the entire data set, and pairs presenting an r>0.65 were considered redundant. In such cases, the item considered most clear in wording by the Steering Committee was retained. In addition, items only relevant to a subgroup of patients, such as those relating to pregnancy (only applicable to women of childbearing age) or to professional activity (only applicable to people in work), were eliminated. The finalised questionnaire was translated from French into English through two independent forward and backward translations and reconciliation of the translated texts.[26]

Preliminary validation

All patients for whom both patient and physician questionnaires had been received were considered. Missing values were replaced according to a Missing at Random hypothesis. When the proportion of missing data was <5%, individual missing items were replaced with the median value of the corresponding

Table 1 Patient characteristics

	RA (n=432)	axSpA (n=240)	Total (n=672)
Age (years)	n=368 58.3±13.1	n=207 47.0±13.2	n=575 54.2±14.2
Gender	n=373	n=208	n=581
Female	276 (74.0%)	94 (45.2%)	370 (63.7%)
Male	97 (26.0%)	114 (54.8%)	211 (36.3%)
Professional activity	n=424	n=237	n=661
In employment	162 (38.2%)	167 (70.5%)	329 (49.8%)
Student	2 (0.5%)	1 (0.4%)	3 (0.5%)
Unemployed	8 (1.9%)	19 (8.0%)	27 (4.1%)
Retired	201 (47.4%)	30 (12.7%)	231 (34.9%)
Other	51 (12.0%)	20 (8.4%)	71 (10.7%)
Education level	n=427	n=238	n=665
Primary	77 (18.0%)	11 (4.6%)	88 (13.2%)
Secondary	219 (51.3%)	134 (56.3%)	353 (53.1%)
Tertiary	131 (30.7%)	93 (39.1%)	224 (33.7%)
Disease duration (years)	n=358 13.1±11.4	n=203 13.8±10.6	n=561 13.4±11.1
Disease activity	n=427	n=236	
DAS28	2.6±1.2	–	–
BASDAI	–	3.3±2.2	–
Physician global assessment of disease activity (NRS)	n=419 2.75±2.12	n=232 3.44±2.41	n=651 3.00±2.25
Patient global assessment of disease activity (NRS)	n=382 3.03±2.45	n=216 4.27±2.61	n=598 3.48±2.58
Treatments	n=326	n=238	n=564
None	5 (1.5%)	7 (2.9%)	12 (2.1%)
Corticosteroids alone	6 (1.8%)	–	6 (1.1%)
NSAIDs alone	–	36 (15.1%)	36 (6.4%)
Synthetic DMARDs ± corticosteroids	61 (18.7%)	–	61 (10.8%)
Synthetic DMARDs ± NSAIDs	–	15 (6.3%)	15 (2.7%)
Biological DMARDs (alone or in combination)	252 (77.3%)	173 (72.7%)	425 (75.4%)
Other	2 (0.6%)	7 (2.9%)	9 (0.7%)

Data are presented as mean values±SD for continuous variables, and as frequency counts (%) for categorical variables.
axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DAS28, 28-item Disease Activity Score; DMARD, disease-modifying antirheumatic drug; NRS, numerical rating scale; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis.

Table 2 Mean scores for each item of the FAIR scale in patients with RA or axSpA

	RA n=432	axSpA n=240	Total population n=672	p Value
Fears related to the progression and consequences of the disease				
I am afraid of suffering like I did before	6.4±3.4	6.9±3.3	6.6±3.4	0.082
I am afraid that my disease will progress quickly	5.0±3.4	6.0±3.2	5.4±3.4	<0.001
I am afraid that my spine or some of my bones will fuse together	4.1±3.6	6.4±3.4	5.0±3.7	<0.001
I am afraid I won't get any help if I lose my autonomy	4.4±3.7	4.9±3.7	4.6±3.7	0.066
I am afraid I won't be able to cope with my daily tasks	6.3±3.2	6.9±2.9	6.5±3.1	0.028
I am afraid I will be considered as a disabled person	4.9±3.8	5.4±3.7	5.1±3.7	0.118
I am afraid that a time will arrive when no treatment will work for me anymore	5.2±3.8	6.3±3.7	5.6±3.8	<0.001
Fears related to treatment				
I am afraid of the side effects of treatment for my disease	6.0±3.2	6.3±3.1	6.1±3.2	0.245
I am afraid that treatments for my disease may cause cancer	4.1±3.6	4.8±3.5	4.4±3.6	0.013
I am afraid that treatments for my disease will become less effective	5.7±3.3	6.6±2.9	6.0±3.2	0.001

Probability values were determined using the Wilcoxon signed-rank test.
axSpA, axial spondyloarthritis; FAIR, Fear Assessment in Inflammatory Rheumatic diseases; RA, rheumatoid arthritis.

variable. When the proportion exceeded 5%, multiple imputation methods based on Markov chains and Monte Carlo simulations were used. Score distribution was assessed using mean±SD and median with IQR scores for each disease population.

The factorial structure of the questionnaire was determined using principal component analysis, and eigenvalues calculated. A confirmatory factor analysis was then performed to determine goodness of fit, restricted to dimensions with eigenvalue >1.[27] Internal coherence was assessed with Cronbach's α coefficient.[28] Test–retest stability of the PRO was evaluated by determining the Pearson's correlation coefficient for total scores between two questionnaires completed at 2 weeks' interval by 30 respondents. Coefficients >0.70 were considered to represent a strong correlation, and coefficients 0.50–0.70, a moderate correlation. The discriminative validity of the PRO was assessed by evaluating the relationship between the scores and other study variables expected to be related to the PRO score, such as HADS anxiety score, helplessness (AHI score) or disease activity score. Anxiety/depression and helplessness were expected to be moderately to strongly correlated with fears, whereas disease activity was expected to be only moderately correlated.

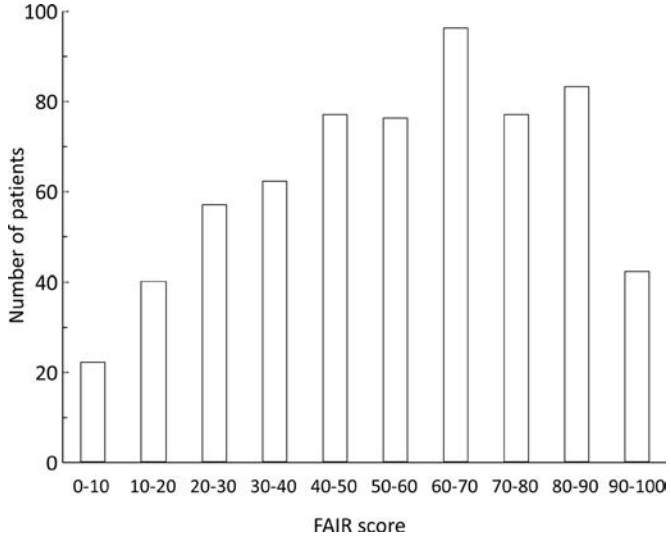


Figure 1 Distribution of FAIR (Fear Assessment in Inflammatory Rheumatic diseases) scores in the full study population. The full study population includes 368 patients with rheumatoid arthritis (RA) and 207 with axial spondyloarthritis (axSpA).

Identification of patient clusters and characteristics associated with fears

Subgroups of patients were identified according to their fear scores using descending cluster analysis (Ward method[29]). Optimal thresholds to distinguish between high and low fear score clusters were identified using receiver operating characteristic (ROC) curves based on the Youden index (optimal sensitivity and specificity).[30]

Univariate, then multivariate logistic regression was used to identify patient variables (including demographic, social and economic characteristics; disease status, and anxiety/depression and helplessness levels) independently associated with the highest compared with the lowest fear score cluster. Variables identified in the univariate analysis (p<0.20) were entered into a backward stepwise multiple logistic regression model.

All statistical analyses were performed using SAS V.9.2.

Ethics

The study was performed in accordance with Good Epidemiological Practice[31] and relevant French guidelines for patient surveys. Verbal informed consent was obtained from all participating patients.

RESULTS

Participants

All 1618 rheumatologists in France were contacted: 134 agreed to participate in the study, and 100 enrolled at least 1 patient. Twenty were exclusively community based, 51 exclusively hospital based and the remaining 29 had a mixed practice. A total of 796 patients were enrolled, of whom 672 (84.4%) were retained for analysis (see online supplementary figure 1). Patient characteristics are presented in table 1. Disease was moderately active, and use of biologics exceeded 70% in both the RA and axSpA patient populations.

Finalisation of the Fear Assessment in Inflammatory Rheumatic diseases questionnaire

Factorial analysis of the initial 44-item questionnaire (which dealt with both fears and opinions) revealed two highly

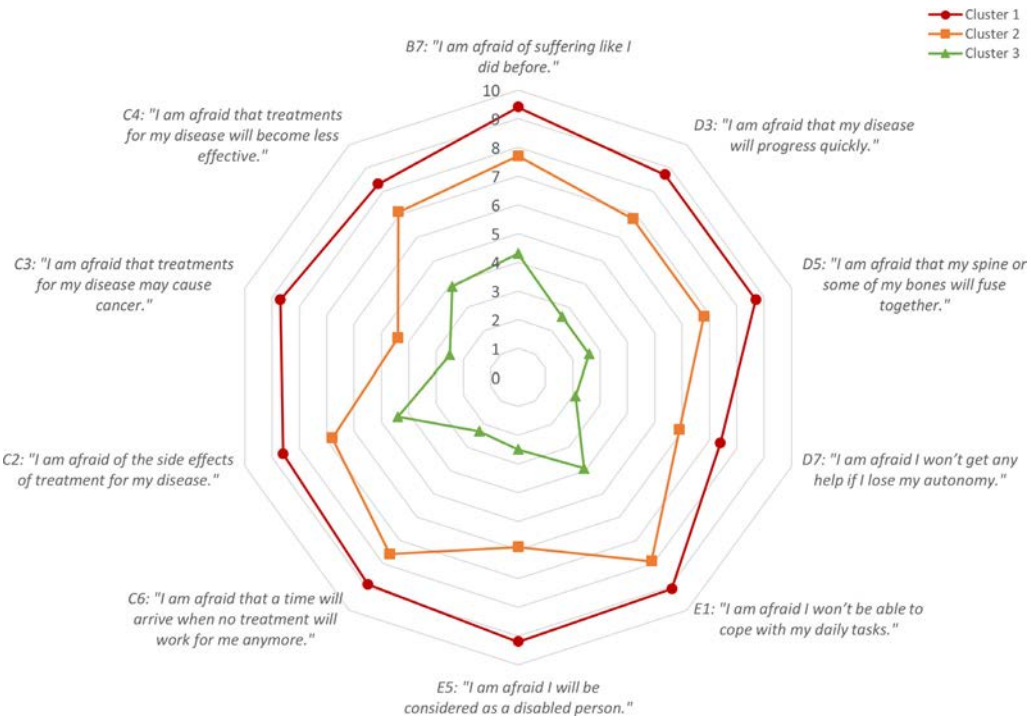


Figure 2 Distribution of FAIR (Fear Assessment in Inflammatory Rheumatic diseases) scores in patients with rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA). Red: high fear cluster, n=116; orange: moderate fear cluster, n=276; green: low fear cluster, n=280.

correlated dimensions related to fears: one to disease outcome, and the other to treatment. After exclusion of redundant items with interitem correlation coefficients >0.65 (see online supplementary table 1), the final scale comprised 10 items (table 2 and online supplementary tables 2 and 3). Each item is scored on a 10-point numerical rating scale ranging from 0 (no fear) to 10 (strong fear). The total score ranges from 0 to 100 and was calculated as the sum of the 10 individual item scores.

Psychometric validation

Internal consistency was high (Cronbach's α coefficient: 0.89). Principal component analysis identified a single dimension (eigenvalue: 5.1), which accounted for 51.2% of variance in the item scores. Confirmatory factor analysis matching the data to a unidimensional factorial structure revealed a goodness-of-fit index of 0.91. Twenty-eight patients (13 RA and 15 axSpA) provided two questionnaires completed 2 weeks apart. The test–retest correlation coefficient was ≥0.81. Total FAIR (Fear Assessment in Inflammatory Rheumatic diseases) scores were correlated with HADS anxiety (r=0.47; p<0.001) and depression (r=0.40; p<0.001) scores, and with AHI scores (r=0.50; p<0.001) (see online supplementary figure 2).

Distribution of scores in patients with RA and axSpA

The mean and median FAIR scores were 54.9±24.9 and 57 (IQR: 35–75), respectively. Scores were higher in patients with axSpA (60.5±22.9; 65 (43–79)) than in patients with RA (51.8±25.4; 52 (33–71)). The distribution of PRO scores for the full data set is presented in figure 1. The mean item scores on the FAIR scale are presented in table 2 for the total study population, for patients with RA and for patients with axSpA. Mean fear scores were consistently higher for all items in patients with axSpA compared with those with RA.

Subgroups of patients

Hierarchical cluster analysis identified three groups of patients characterised by high (cluster 1; n=116; 17.2%; mean score 87.0±7.9), moderate (cluster 2; n=276; 41.1%; mean score 65.8±11.4) and low levels of fear (cluster 3; n=280; 41.7%; mean score 31.1±14.7) (figure 2). These three clusters accounted for 68.3% of the variance in the data set. The most discriminating cut-off threshold to distinguish the high fear cluster from the other two was 77 (sensitivity: 0.90; specificity: 0.91). The most sensitive cut-off threshold to distinguish the low fear cluster from the other two was 51 (sensitivity: 0.92; specificity: 0.93). The area under the ROC curve was >0.97 in both cases (see online supplementary figure 3).

Multiple logistic regression analysis was used to determine patient characteristics independently associated with high fear scores, discriminating between patients in cluster 1 and those in cluster 3 (figure 3). Cluster 1 (high fear scores) was associated with higher global rating of disease activity by the patient, high AHI helplessness scores and high HADS anxiety and depression scores. With respect to sociodemographic variables, low education level, not working and living alone were also associated with higher FAIR score, as was immigrant status. No significant effects of disease type (axSpA vs RA) or age were observed. With respect to the patients in cluster 2 (moderate fear scores), the same variables were identified, although the ORs were lower.

DISCUSSION

This large national survey of patients with RA or axSpA generated two principal results. First, almost one-fifth (17.2%) of evaluated patients had high fear scores, despite both diseases being typically well managed, and these scores were associated with psychological distress. Thus, the fears identified in this study may reflect psychological distress, and need to be addressed even in patients who have moderate to low disease activity. Second, we have developed the FAIR questionnaire: a disease-specific,

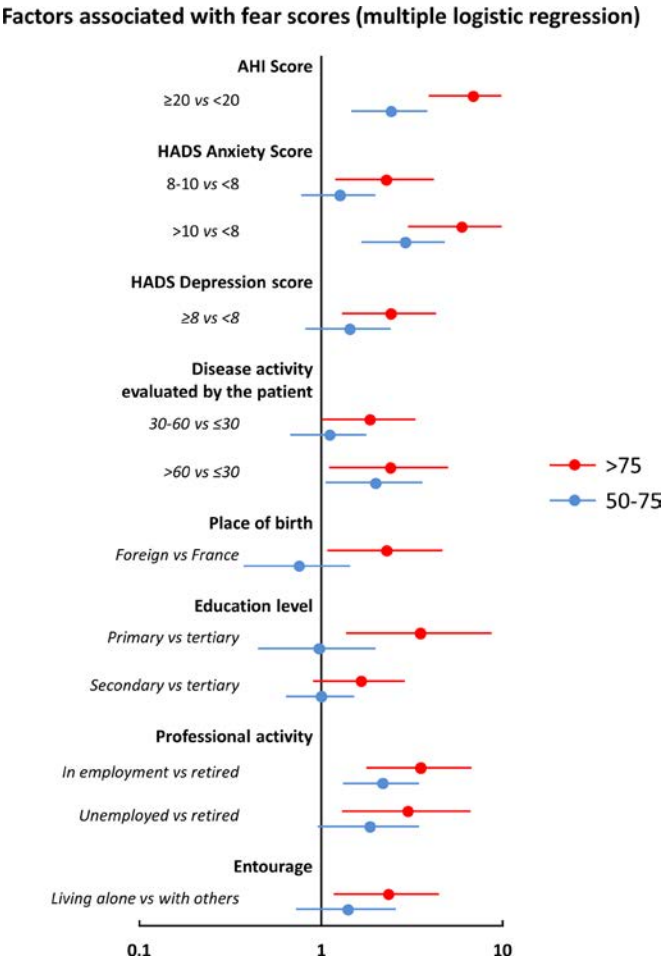


Figure 3 Variables independently associated with a high or moderate FAIR (Fear Assessment in Inflammatory Rheumatic diseases) score versus a low score in patients with rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA). High scores indicate those >75 (shown in red); moderate scores, 50–75 (shown in blue); and low scores, <50. Data are presented as ORs (95% CIs). AHI, Arthritis Helplessness Index; HADS, Hospital Anxiety and Depression Scale.

psychometrically validated PRO to measure disease and treatment-related fears in patients with RA or axSpA. This instrument demonstrated acceptable psychometric properties: notably unidimensionality, high internal coherence, good discriminant validity and adequate test–retest stability. The FAIR is short (10 items), simple to score and may be a useful tool both in routine practice and clinical trials.

The strengths of this study include the size of the study population, the high level of patient involvement in the development of the questionnaire and the psychometric validation[16–20] of this instrument in line with the recommended guidelines. Limitations include a potential cultural bias, since the items were derived from a qualitative survey of patients in France, and potential redundancy with existing disease-specific PROs for CIRDs.[12 32–34] These aspects will need to be evaluated in future studies. Although some questions within the questionnaire may seem redundant, statistical tests were used to remove truly redundant questions, and all questions underwent validation with patients.

In this study, it was possible to classify patients according to their level of fear using the FAIR score. Fear scores did not appear to be related to objective disease activity scores (DAS28(ESR) or BASDAI), although patients with high perceived disease activity (>6) were more frequently classified in the high fear cluster. In contrast, a strong association was observed between FAIR scores and scores on the AHI (≥20) or HADS (≥10 for anxiety and ≥8 for depression), all of which are non-specific markers of psychological distress.

Patients with RA commonly present a higher level of psychological distress compared with the general population.[35 36] In agreement with this, we observed a robust association between fears and non-specific measures of psychological distress, such as the AHI, the HADS anxiety score and, to a lesser extent, the HADS depression score. Moreover, the fears expressed by our patients are likely to represent specific expressions of psychological distress in inflammatory rheumatic diseases. This would suggest that the FAIR questionnaire could be employed to measure psychological distress in a disease-specific way in patients with RA or axSpA. To this end, it might be beneficial to compare the FAIR questionnaire with existing generic scales, such as the mental component score of the SF-36 or SF-12 (36-Item and 12-Item Short Form Health Survey),[10] or the anxiety and depression items of the Arthritis Impact Measurement Scales,[12] in future studies. The FAIR instrument will also need to be tested in independent populations to verify its robustness and psychometric validity.

An association, although less marked, was also observed between FAIR scores and disease activity as rated by the patient. Four sociodemographic variables were also associated with high fear scores, namely low education level, living alone, being born outside France and either being in or seeking employment. Low education levels may be associated with lower access to, or more limited understanding of, information about the disease; this may also be the case for immigrants. Patients living alone may lack adequate social support for coping with stressful situations, and patients in employment or seeking employment may be particularly worried about the impact of their disease on their future career and income. On the other hand, age, gender, diagnosis (RA or axSpA) and treatment were not independently associated with high fear scores. Previous studies have identified female gender, lack of social support and a lower educational level as being associated with anxiety and depression (or both) in patients with RA.[37–39]

The FAIR questionnaire may be a useful PRO in several contexts. First, it may be helpful for physicians taking care of patients with RA and axSpA to evaluate the levels of fear and psychological distress in their patients, in order to provide an appropriate level of psychological support and to initiate a physician–patient dialogue to dispel unwarranted fears and facilitate adaptive coping. In clinical research, the questionnaire may be useful for investigating differences in psychological distress between patient groups, and to provide a basis for explaining such differences. Finally, the FAIR could be included in clinical trial protocols to measure the impact of specific interventions on psychological distress; however, this would first require an assessment of the instrument's sensitivity to change. In this context, a disease-specific PRO might be more sensitive than a non-specific tool such as the HADS.

Author affiliations
[1]Sorbonne Universités, UPMC Univ Paris 06,Institut Pierre Louis d'Epidémiologie et de Santé Publique (UMRS 1136), GRC-UPMC 08 (EEMOIS), Paris, France
[2]Rheumatology Department, Hôpital Pitié Salpêtrière, AP-HP, Paris, France
[3]Department of Social Epidemiology, Sorbonne Universités, UPMC Univ Paris 06, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (UMRS 1136), Paris, France
[4]Department of Rheumatology, CHU de la Cavale-Blanche, Brest, France

[5]Université de Brest, LabEx IGO, UMR1227, Lymphocytes B et Autoimmunité, Brest, France
[6]Department of Rheumatology, Hôpital Cochin, AP-HP, Paris, France
[7]UCB Pharma, Colombes, France
[8]Arthritis Fondation Courtin, Neuilly-sur-Seine, France
[9]AXONAL-BIOSTATEM, Nanterre, France
[10]Sorbonne Universités, UPMC Univ Paris 06, INSERM, Paris, France
[11]Department of Rheumatology, Hôpital Saint-Antoine, AP-HP, DHU i2B, Paris, France

Acknowledgements The authors thank the patients, the investigators and their teams who took part in this study. The authors also acknowledge Gabrielle von Krause (patient research partner; Paris, France) for developing the wording and content of the questionnaire; Susanne Wiegratz (UCB Pharma GmbH, Monheim am Rhein, Germany) for publication coordination; and Sam Fraser, PhD (Costello Medical Consulting Ltd, Cambridge, UK) for editorial assistance in preparing this manuscript for publication, based on the authors' input and direction.

Contributors All authors were involved in drafting and in final approval of the publication, and revising it critically for important intellectual content.

Funding UCB Pharma and Fondation Arthritis (France).

Competing interests LG, PC, AS, CH, CD, ST, FB: no competing interests. GC and J-MJ are employees of UCB Pharma; TdC was an employee of UCB Pharma at the time of the study; VS and FR-M are employees of Fondation Arthritis.

Ethics approval The Ethics Committee of the St Antoine Hospital, Paris (session of 7 October 2014), the National Advisory Committee on Medical Research Information (CCTIRS) and the French national data protection agency (CNIL).

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Matcham F, Scott IC, Rayner L, *et al*. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. *Semin Arthritis Rheum* 2014;44:123–30.
2 Pouchot J, Le Parc JM, Queffelec L, *et al*. Perceptions in 7700 patients with rheumatoid arthritis compared to their families and physicians. *Joint Bone Spine* 2007;74:622–6.
3 Riemsma RP, Taal E, Rasker JJ. Perceptions about perceived functional disabilities and pain of people with rheumatoid arthritis: differences between patients and their spouses and correlates with well-being. *Arthritis Care Res* 2000;13:255–61.
4 Bacconnier L, Rincheval N, Flipo RM, *et al*. Psychological distress over time in early rheumatoid arthritis: results from a longitudinal study in an early arthritis cohort. *Rheumatology* 2015;54:520–7.
5 Bruce TO. Comorbid depression in rheumatoid arthritis: pathophysiology and clinical implications. *Curr Psychiatry Rep* 2008;10:258–64.
6 Lok EY, Mok CC, Cheng CW, *et al*. Prevalence and determinants of psychiatric disorders in patients with rheumatoid arthritis. *Psychosomatics* 2010;51:338–338.e8.
7 Berenbaum F, Chauvin P, Hudry C, *et al*. Fears and beliefs in rheumatoid arthritis and spondyloarthritis: a qualitative study. *PLoS One* 2014;9:e114350.
8 Hamilton-West KE, Quine L. Living with ankylosing spondylitis: the patient's perspective. *J Health Psychol* 2009;14:820–30.
9 Lütze U, Archenholtz B. The impact of arthritis on daily life with the patient perspective in focus. *Scand J Caring Sci* 2007;21:64–70.
10 Ware JE, Kosinski M, Bayliss MS, *et al*. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the medical outcomes study. *Med Care* 1995;33:AS264–79.
11 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
12 Meenan RF, Gertman PM, Mason JH. Measuring health status in arthritis. The arthritis impact measurement scales. *Arthritis Rheum* 1980;23:146–52.
13 Pincus T, Swearingen C, Wolfe F. Toward a multidimensional health assessment questionnaire (MDHAQ): assessment of advanced activities of daily living and psychological status in the patient-friendly health assessment questionnaire format. *Arthritis Rheum* 1999;42:2220–30.
14 Kilic L, Erden A, Bingham CO, *et al*. The reporting of patient-reported outcomes in studies of patients with rheumatoid arthritis: a systematic review of 250 articles. *J Rheumatol* 2016;43:1300–5.
15 Stolwijk C, Castillo-Ortiz JD, Gignac M, *et al*. Importance of contextual factors when measuring work outcome in ankylosing spondylitis: a systematic review by the OMERACT worker productivity group. *Arthritis Care Res* 2015;67:1316–27.
16 European medicines agency. *Committee for medicinal products for human use (CHMP): reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products*. London: EMA, 2005.
17 US department of health and human services and food and drug administration. *Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims*. Silver Spring: FDA, 2009.
18 Kirwan JR, Bartlett SJ, Beaton DE, *et al*. Updating the OMERACT filter: implications for patient-reported outcomes. *J Rheumatol* 2014;41:1011–5.
19 Mokkink LB, Terwee CB, Patrick DL, *et al*. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res* 2010;19:539–49.
20 Reeve BB, Wyrwich KW, Wu AW, *et al*. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. *Qual Life Res* 2013;22:1889–905.
21 Aletaha D, Neogi T, Silman AJ, *et al*. 2010 Rheumatoid arthritis classification criteria: an american college of rheumatology/european league against rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569–81.
22 Zeidler H, Amor B. The assessment in spondyloarthritis international society (ASAS) classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general: the spondyloarthritis concept in progress. *Ann Rheum Dis* 2011;70:1–3.
23 Nicassio PM, Wallston KA, Callahan LF, *et al*. The measurement of helplessness in rheumatoid arthritis. The development of the arthritis helplessness index. *J Rheumatol* 1985;12:462–7.
24 Garrett S, Jenkinson T, Kennedy LG, *et al*. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994;21:2286–91.
25 Prevoo ML, van 't Hof MA, Kuper HH, *et al*. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44–8.
26 Wild D, Grove A, Martin M, *et al*. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR task force for translation and cultural adaptation. *Value Health* 2005;8:94–104.
27 Jöreskog KG. A general approach to confirmatory maximum likelihood factor analysis. *Psychometrika* 1969;34:183–202.
28 Cronbach LJ. Coefficient alpha and the internal structure of tests. *Psychometrika* 1951;16:297–334.
29 Ward JH. Hierarchical grouping to optimize an objective function. *J Am Stat Assoc* 1963;58:236–44.
30 Youden WJ. Index for rating diagnostic tests. *Cancer* 1950;3:32–5.
31 Council for International Organizations of Medical Sciences. *International ethical guidelines for epidemiological studies*. Geneva: CIOMS, 2008.
32 Cleanthous S, Isenberg DA, Newman SP, *et al*. Patient uncertainty questionnaire-rheumatology (PUQ-R): development and validation of a new patient-reported outcome instrument for systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) in a mixed methods study. *Health Qual Life Outcomes* 2016;14:33.
33 Newman S, Fitzpatrick R, Lamb R, *et al*. Patterns of coping in rheumatoid arthritis. *Psychol Health* 1990;4:187–200.
34 Gossec L, Dougados M, Rincheval N, *et al*. Elaboration of the preliminary rheumatoid arthritis impact of disease (RAID) score: a EULAR initiative. *Ann Rheum Dis* 2009;68:1680–5.
35 Dickens C, McGowan L, Clark-Carter D, *et al*. Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. *Psychosom Med* 2002;64:52–60.
36 Pincus T, Griffith J, Pearce S, *et al*. Prevalence of self-reported depression in patients with rheumatoid arthritis. *Br J Rheumatol* 1996;35:879–83.
37 Zyrianova Y, Kelly BD, Gallagher C, *et al*. Depression and anxiety in rheumatoid arthritis: the role of perceived social support. *Ir J Med Sci* 2006;175:32–6.
38 Evers AW, Kraaimaat FW, Geenen R, *et al*. Longterm predictors of anxiety and depressed mood in early rheumatoid arthritis: a 3 and 5 year followup. *J Rheumatol* 2002;29:2327–36.
39 Dirik G, Karanci AN. Psychological distress in rheumatoid arthritis patients: an evaluation within the conservation of resources theory. *Psychol Health* 2010;25:617–32.

EXTENDED REPORT

Influence of disease activity and medications on offspring birth weight, pre-eclampsia and preterm birth in systemic lupus erythematosus: a population-based study

Carina Götestam Skorpen,[1,2] Stian Lydersen,[3] Inge-Margrethe Gilboe,[4] Johan Fredrik Skomsvoll,[5] Kjell Å Salvesen,[6,7] Øyvind Palm,[4] Hege Suorza Svean Koksvik,[5] Bente Jakobsen,[5] Marianne Wallenius[1,5]

Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-211641).

For numbered affiliations see end of article.

Correspondence to
Carina Götestam Skorpen, Department of Rheumatology, Ålesund Hospital, 6026 Ålesund, Norway;
carina.skorpen@ntnu.no

Received 12 April 2017
Revised 21 October 2017
Accepted 22 October 2017
Published Online First 1 November 2017

ABSTRACT

Objectives Exploring the associations between disease activity and medications with offspring birth weight, pre-eclampsia and preterm birth in systemic lupus erythematosus (SLE).

Methods Data from the Medical Birth Registry of Norway (MBRN) were linked with data from RevNatus, a nationwide observational register recruiting women with inflammatory rheumatic diseases. Singleton births in women with SLE included in RevNatus 2006–2015 were cases (n=180). All other singleton births registered in MBRN during this time (n=498 849) served as population controls. Z-score for birth weight adjusted for gestational age and gender was calculated. Disease activity was assessed using Lupus Activity Index in Pregnancy. We compared z-scores for birth weight, pre-eclampsia and preterm birth in cases with inactive disease, cases with active disease and population controls.

Results Z-scores for birth weight in offspring were lower in inactive (−0.64) and active (−0.53) diseases than population controls (−0.11). Inactive disease did not predict pre-eclampsia while active disease yielded OR 5.33 and OR 3.38 compared with population controls and inactive disease, respectively. Preterm birth occurred more often in inactive (OR 2.57) and active (OR 8.66) diseases compared with population controls, and in active compared with inactive disease (OR 3.36).

Conclusions SLE has an increased odds for low birth weight and preterm birth, amplified by active disease. The odds for pre-eclampsia is elevated in active, but not inactive disease. This calls for tight follow-up targeting inactive disease before and throughout pregnancy.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic rheumatic disease often affecting women in fertile age. In SLE, there is an increased risk of unfavourable pregnancy outcomes including low birth weight and preterm birth and complications like pre-eclampsia, even though there is evidence for less elevated risk over the last decades.[1] Pre-eclampsia is one of the risk factors for preterm birth. The increased risk of pre-eclampsia including early-onset pre-eclampsia (before 34 weeks) in SLE may be independent of traditional risk factors such as pregestational hypertension and body mass index (BMI).[2] High disease activity and flare shortly before or during pregnancy are factors predictive for complications,[3–5] whereas no or low disease activity is favourable.[6] A recent population-based study reported lower mean birth weight and gestational age in both first and subsequent births in women with SLE compared with references.[7] Low birth weight caused by intrauterine growth restriction is associated with an increased risk of cardiovascular disease and diabetes in the offspring.[8] Pre-eclampsia, preterm birth and low offspring birth weight are events associated with a future higher risk of maternal cardiovascular disease[9] and death.[10] Prednisolone use in pregnancy has been associated with preterm birth and a lower birth weight.[11] In SLE, prednisolone is commonly used to treat disease flares, and confounding by indication may explain this finding. Most studies investigating the influence of disease activity on pregnancy outcomes have found high disease activity or disease flare to be risk factors for adverse pregnancy outcomes. To our knowledge, prospective studies comparing pregnancy outcomes in SLE women with inactive disease, SLE women with active disease and population controls have not been reported. We regard birth weight adjusted for gestational age and gender (z-score) as the relevant birth weight outcome in this context. The aim of this study was to explore the possible associations of disease activity and medications with offspring birth weight z-score and the occurrence of pre-eclampsia and preterm birth in women with SLE.

PATIENTS AND METHODS

Study population

In this population-based cohort, we linked data from the Medical Birth Registry of Norway (MBRN) with data from RevNatus. MBRN is a national health registry with mandatory registration of variables on all births in Norway. It includes information about maternal health before and during pregnancy as well as maternal and neonatal complications during pregnancy and birth. The variables were decided by consensus among obstetricians, neonatologists and epidemiologists. Since December 1998,[12] pre-pregnant maternal diseases including rheumatic diseases have been coded according to the International

To cite: Skorpen CG, Lydersen S, Gilboe I-M, *et al*. *Ann Rheum Dis* 2018;**77**:264–269.

Table 1 Characteristics of patients (SLE) and population controls, reported as n (%) unless specified as mean (SD)

Characteristic	SLE	Population controls	P value
Number of deliveries	180	498 849	
Maternal age (years), mean (SD)	31.5 (5.0)	30.4 (5.1)	0.004
<35	138 (76.7)	402 064 (80.6)	
≥35	42 (23.3)	96 569 (19.4)	
Missing	–	–	
Parity			0.91
No children	77 (42.8)	209 978 (42.1)	
≥1 child	103 (57.2)	288 871 (57.1)	
Missing	–	–	
Smoking in pregnancy	12 (6.9)	47 137 (11.2)	0.09
Missing	6	79 171	
BMI first trimester, mean (SD)	23.8 (4.9)	24.3 (4.8)	0.30
Underweight (<18.5)	7 (8.3)	8298 (4.1)	
Normal weight (18.5–24.9)	50 (59.5)	123 903 (61.5)	
Overweight (≥25)	27 (32.1)	69 294 (34.4)	
Missing	96	297 354	

BMI, body mass index; SLE, systemic lupus erythematosus.

Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).

RevNatus is a nationwide Norwegian multicentre, prospective observational register recruiting women with inflammatory rheumatic diseases who plan pregnancy or are pregnant. Women 18 years or older are included, with follow-up in each trimester and at 6 weeks, 6 and 12 months after birth. All women are diagnosed by a specialist in rheumatology prior to inclusion. Information on obstetric history, disease activity and medications as well as maternal and neonatal outcomes including complications is registered. In the present study, singleton births recorded in MBRN 2006–2015 were eligible for inclusion. Births among women with the diagnosis of SLE recorded in MBRN (ICD-10 codes M32.1, M32.8 and M32.9) *and* included in RevNatus formed the patient group (n=180). Population controls were all other singleton births registered in MBRN during the same period (n=498 849), but excluding births among women with any rheumatic inflammatory disease (n=2492) according to ICD-10 diagnoses (online supplementary figure S1). The 2015 age cohort was excluded from the population controls as the registration of ICD diagnoses of maternal pre-pregnant disease was not completed. One woman could have several births during the study period. This applied to 28 (15.6 %) of 180 women in the patient group and an unknown proportion of the women in the control population.

Ethics

All women signed a written informed consent before inclusion. Access to data from MBRN was granted in September 2016 (MBRN assignment 15-1819).

Variables

For both patients and population controls, data on maternal age, parity, smoking and BMI were derived from MBRN, as were data on newborns and complications including pre-eclampsia,[13 14] preterm birth (<37 gestational weeks) and very preterm birth (<34 gestational weeks). BMI was included as a variable in MBRN in 2012 and reported by 40% of the birth institutions, resulting in high missing numbers. For the patient group, educational status, prior obstetric history and disease-specific information were retrieved from RevNatus. Fulfilment of the 1997 American College of Rheumatology criteria for classification of SLE required ≥4 criteria.[15] A positive test for lupus anticoagulant, anticardiolipin antibody IgG and antibeta2 glycoprotein I IgG was defined according to thresholds for positivity at the time of the test.

Assessment of disease activity

Disease activity was assessed by the Lupus Activity Index in Pregnancy (LAI-P), a modification of the Lupus Activity Index (LAI) validated for use in pregnancy.[16] LAI-P is described in detail elsewhere.[17] Briefly, disease activity is assessed on a scale from 0 (inactive disease) to 2.6 (very high disease activity), with a score above 0.5 considered moderate disease activity. It is a composite score, including items describing general and organ-specific clinical manifestations, current medication and certain laboratory findings. LAI-P was assessed in each trimester and at 6 weeks after birth, and dichotomised to inactive disease (LAI-P=0) and active disease of any severity (LAI-P>0). There were missing data on disease activity at all visits, and most frequently among the preterm (39% missing) and very preterm (50% missing) births in the third trimester. The data were not missing completely at random, as many of these women did not attend the third trimester visit due to birth before scheduled visit. Data on disease activity were more complete in the second trimester (missing in 20% of term and 6% of preterm outcomes).

Calculation of birth weight z-score adjusted for gestational age and gender

Recorded pregnancy outcomes in MBRN included birth weight (grams), gender and gestational age at delivery in days based on a mid-trimester ultrasound examination. Birth weight is influenced by gestational age and gender, differs from country to country and has secular changes. Accordingly, z-score for birth weight was calculated using Norwegian birth weight by gestational age standards covering 20–44 completed weeks, separately for males and females.[18] The z-scores were calculated using gestational age in days, with linear interpolation between weeks.

Statistical analyses

Group comparisons were performed using independent t-test for continuous variables and the Pearson χ^2 test or the unconditional z-pooled test for categorical variables.[19] We used linear regression with z-score as dependent variable, and logistic regression for dichotomous-dependent variables (pre-eclampsia and preterm birth). As covariates, we compared population controls with cases with inactive disease (LAI-P=0) and cases with active disease (LAI-P>0) in the second trimester. We carried out the analyses unadjusted, and adjusted for maternal age (<35 years/≥35 years), parity (no birth/≥1 birth) and smoking in pregnancy (yes/no). We also carried out analyses for first and subsequent births separately. Separate analyses were performed concerning use of prednisolone (yes/no) in the second trimester, and adjusting for hydroxychloroquine (yes/no) and azathioprine (yes/no). Missing values were handled by available case analysis. Two-sided P values less than 0.05 were considered statistically significant, and 95% CIs are reported where relevant. The statistical analyses were performed using SPSS V.22.

Table 2 Clinical characteristics of all patients (SLE), and grouped according to disease activity in second trimester, reported as n (%) unless specified as mean (SD)

Characteristic	SLE (total)	Inactive disease (LAI-P=0)	Active disease (LAI-P>0)	Not registered disease activity	P value*
Number of deliveries	180	85	63	32	
Maternal age, mean (SD)	31.5 (5.0)	31.9 (4.6)	31.3 (5.5)	30.8 (4.9)	0.47
<35	138 (76.7)	65 (76.5)	47 (74.6)	26 (81.3)	
≥35	42 (23.3)	20 (23.5)	16 (25.4)	6 (18.8)	
Missing	–	–	–	–	
Nullipara	77 (42.8)	32 (37.6)	29 (46.0)	16 (50.0)	0.39
Missing	–	–	–	–	
Smoking in pregnancy	12 (6.9)	2 (2.4)	7 (11.1)	3 (10.3)	0.032†
Missing	6	3	–	3	
BMI first trimester, mean (SD)	23.8 (4.9)	22.7 (4.4)	24.7 (5.8)	24.5 (3.9)	0.11
<18.5	7 (8.0)	6 (15.0)	1 (3.4)	0	
18.5–25	52 (59.1)	24 (60.0)	19 (65.5)	9 (47.4)	
≥25	29 (33.0)	10 (25.0)	9 (31.0)	10 (52.6)	
Missing	92	45	34	13	
Educational level					0.44
Low‡	13 (7.4)	6 (7.2)	5 (8.1)	2 (6.5)	
Intermediate§	46 (26.1)	18 (21.7)	19 (30.6)	9 (29.0)	
High¶	117 (66.5)	59 (71.1)	38 (61.3)	20 (64.5)	
Missing	4	2	1	1	
ACR criteria fulfilled**	114 (82.3)	51 (77.3)	47 (90.4)	16 (84.2)	0.10
Missing	43	11	19	13	
Disease duration, mean (SD)	8.7 (6.2)	8.8 (5.6)	8.6 (6.2)	8.3 (7.4)	0.86
Missing	9	5	2	2	
Prior pregnancy loss	30 (18.0)	13 (16.9)	15 (24.2)	2 (7.1)	0.39
Missing	13	8	1	4	
Prior pre-eclampsia	13 (7.2)	6 (7.1)	6 (9.5)	1 (3.1)	0.53
Missing	2	1	1	–	
Positive LAC	29 (23.6)	14 (21.9)	12 (27.9)	3 (18.8)	0.63
Missing	57	21	20	16	
Positive aCL IgG	13 (7.4)	8 (9.8)	5 (8.1)	0	0.73
Missing	5	3	1	1	
Positive Aβ2GPI IgG	9 (5.0)	3 (6.1)	6 (18.8)	0	0.089†
Missing	83	36	31	16	
Prior kidney manifestation	40 (35.0)	21 (31.3)	22 (40.0)	7 (33.3)	0.42
Missing	37	18	8	11	

*P value for active compared with inactive disease.
†The unconditional z-pooled exact test.
‡10 years.
§12–13 years.
¶>15 years.
**≥4 criteria according to 1997 American College of Rheumatology diagnostic criteria for SLE.
Aβ2GPI IgG, anti-beta2 glycoprotein I IgG; aCL IgG, anti-cardiolipin IgG; ACR, American College of Rheumatology; BMI, body mass index; LAC, lupus anticoagulant; LAI-P, Lupus Activity Index in Pregnancy; SLE, systemic lupus erythematosus.

RESULTS

Patient recruitment

During 2006–2015, 237 inclusions among 203 women diagnosed with SLE were registered in RevNatus. Of known outcomes (n=223), 5% did not become pregnant, miscarriage was reported in 12%, and 83% resulted in live birth. There were 180 singleton and 6 twin deliveries. Among the singleton births, 26 women had two deliveries and 2 women had three deliveries. The majority (141/180) were included in the first trimester, and the remaining in the second trimester. A total of 498 849 singleton births registered in MBRN during 2006–2014 served as population controls. Maternal mean age among patients was significantly higher compared with population controls (mean difference 1.09 years), a lower proportion smoked, and parity and BMI were similar (table 1).

The cases were grouped according to inactive disease (LAI-P=0) and active disease (LAI-P>0) of any severity in the second trimester. In 32 patients, disease activity was not registered. Clinical characteristics of the disease activity groups and the above group are presented in table 2. The disease activity groups showed no differences of statistical significance except smoking, which was more common in women with active disease.

Between 56.6% and 59.9% of women with SLE had inactive disease during pregnancy and 6 weeks after birth, and less than 10% experienced moderate disease activity or higher (LAI-P>0.5) (table 3). Women delivering preterm mainly had

Table 3 Number and percentages of patients with inactive and active diseases in each trimester and 6 weeks after birth

	Inactive disease n (%)		Active disease n (%)			Missing data on disease activity
	LAI-P=0	Preterm	LAI-P>0	*LAI-P>0.5*	Preterm	n (%)
First trimester	69 (56.6)	10 (14.5)	53 (43.4)	*5 (4.1)*	15 (28.3)	58 (32.2)
Second trimester	85 (57.4)	11 (12.9)	63 (42.6)	*7 (4.7)*	20 (31.7)	32 (17.8)
Third trimester	88 (59.9)	5 (5.7)	59 (40.1)	*8 (5.4)*	15 (25.4)	33 (18.3)
6 weeks pp	90 (59.2)	9 (10.0)	62 (40.8)	*11 (7.2)*	21 (33.9)	28 (15.6)

LAI-P, Lupus Activity Index in Pregnancy; pp, post partum.

active disease (LAI-P>0) on the four scheduled visits (60.0%, 64.5%, 70.0% and 64.7%, respectively). Active disease in the first or second trimester resulted in very preterm birth in 15.4% and 12.9%, respectively, whereas inactive disease resulted in very preterm birth in 6.0% in both groups. The most common disease manifestations in the first and second trimesters were skin (36.0% and 26.3%), joint (26.0% and 17.5%) and haematologic (17.4% and 14.8%). Only 4.2% and 3.6% had active kidney disease, respectively.

Association between SLE disease activity and birth weight z-score, pre-eclampsia and preterm birth

The birth weight z-score was significantly lower in offspring of women with SLE than of population controls (mean difference 0.47). We found significantly lower birth weight z-scores in both disease activity groups compared with population controls, but no significant difference between disease groups (table 4). There was a significantly higher odds of small for gestational age (SGA, ≤10 percentiles) in inactive as well as active diseases compared with population controls (OR 2.45, 95% CI 1.47 to 4.08, P=0.001 and OR 2.66, 95% CI 1.49 to 4.75, P=0.001, respectively). We found no significant differences between disease groups.

Women with SLE had a statistically significantly higher odds of pre-eclampsia and preterm birth compared with population controls, OR 2.70 (95% CI 1.56 to 4.65), P<0.001 and OR 4.03 (95% CI 2.78 to 6.59), P<0.001, respectively. Regarding pre-eclampsia, we found no statistically significant difference between population controls and women with inactive disease, but statistically significantly higher odds when women had active disease. There was substantially higher odds for pre-eclampsia in women with active compared with inactive disease (table 5). Concerning preterm birth, there was a statistically significantly higher odds compared with population controls, both in women with inactive and active diseases. Active disease had a more than twofold increased odds compared with inactive disease. In table 5, OR and P value for pre-eclampsia and preterm birth are shown for inactive disease compared with population controls, for active disease compared with population controls, and for active compared with inactive disease.

We adjusted for factors known to influence outcomes.[7 20 21] The results presented in tables 4 and 5 were substantially unchanged after adjusting for maternal age (<35 years/≥35 years), parity (no birth/≥1 birth) and smoking in pregnancy (yes/no) (data not shown). In separate analyses for first and subsequent births, the observed association was greater for subsequent than for first births for z-score and pre-eclampsia, while this was not the case for preterm birth (online supplementary tables S1 and S2). The P values for the interaction between parity and disease activity were 0.78, 0.24 and 0.51, respectively. Although not considered statistically significant, we find it noteworthy that these effects of parity are observed for both disease activity groups.

Influence of medications on birth weight z-score, preterm birth and pre-eclampsia

Prednisolone was used significantly more often in the second and third trimesters among women with active (58.1% and 57.9%) compared with inactive disease (38.1% and 37.5%). There were no significant differences in the use of hydroxychloroquine or azathioprine between the groups in any of the trimesters, or of prednisolone in the first trimester (51.0% and 38.8%). There was similar use of acetylsalicylic acid (online supplementary table

Table 4 Birth weight z-scores in offspring of population controls, women (SLE) with inactive disease and women (SLE) with active disease*

Group	n	Mean (SD)	Mean difference (95% CI)	P value
Population controls	497 959	−0.11 (0.98)		
Inactive disease (LAI-P=0)	85	−0.64 (0.81)	0.53 (0.32 to 0.74)	<0.001†
Active disease (LAI-P>0)	63	−0.54 (0.90)	0.43 (0.18 to 0.67)	0.001†
			−0.10 (−0.40 to 0.22)	0.53‡

*Unadjusted analysis.
†Compared with population controls.
‡Compared with inactive disease.
LAI-P, Lupus Activity Index in Pregnancy; SLE, systemic lupus erythematosus.

Table 5 Risk of pre-eclampsia and preterm birth in population controls, women (SLE) with inactive disease and women (SLE) with active disease. Logistic regression with adverse event as outcome*

Group	n	n (%)	OR (95 % CI)	P value
Population controls	498 849			
Pre-eclampsia		15 132 (3.0)		
Preterm birth		27 063 (5.5)		
Inactive disease (LAI-P=0)	85			
Pre-eclampsia		4 (4.7)	1.58 (0.58 to 4.31)	0.37†
Preterm birth		11 (12.9)	2.57 (1.37 to 4.85)	0.003†
Active disease (LAI-P>0)	63			
Pre-eclampsia		9 (14.3)	5.33 (2.63 to 10.79)	<0.001†
			3.38 (0.99 to 11.51)	0.052‡
Preterm birth		21 (33.3)	8.66 (5.13 to 14.62)	<0.001†
			3.36 (1.48 to 7.65)	0.004‡

*Unadjusted analysis.
†Compared with population controls.
‡Compared with inactive disease.
LAI-P, Lupus Activity Index in Pregnancy; SLE, systemic lupus erythematosus.

Table 6 Effect of prednisolone use on birth weight z-score, pre-eclampsia and preterm birth*

Mean (SD) or n (%)	No prednisolone n=78	Prednisolone n=68	Mean difference (95% CI) or OR (95% CI)	P value
Z-score	−0.44 (0.84)	−0.77 (0.83)	0.33 (0.05 to 0.61)	0.022
Pre-eclampsia	5 (5.2)	9 (12.5)	2.33 (0.67 to 8.16)	0.19
Preterm birth	11 (11.5)	23 (31.9)	3.36 (1.40 to 8.09)	0.007

*Unadjusted analysis.

S3). Birth weight z-score was statistically significantly lower in offspring of women using prednisolone (mean difference 0.33). There was a substantially higher odds of pre-eclampsia when using prednisolone (OR=2.33), and we found a statistically significant threefold increase in preterm birth (table 6). Results were substantially unchanged after adjusting for hydroxychloroquine (yes/no) and azathioprine (yes/no) (data not shown).

DISCUSSION

We found a lower birth weight z-score in offspring of the disease group compared with population controls, both in inactive and active diseases. The occurrence of SGA was also increased in the disease groups. Our observations of lower birth weight and restricted fetal growth are in accordance with previous studies.[3 7 22 23] There was no evidence of lower birth weight z-score in offspring of women with active compared with inactive disease. There may be several explanations. Our patients had mainly mild disease, with only 4.7% experiencing moderate to high disease activity in the second trimester (LAI-P>0.5). Antiphospholipid syndrome (APS) is a factor independent of disease activity that increases the risk of intrauterine growth restriction and lower birth weight.[24] There were positive anticardiolipin antibodies of similar occurrence in the two disease groups, even though we do not know the occurrence of APS, representing an increased risk for lower birth weight. We found prednisolone use to be a risk factor for a lower birth weight z-score, contributing in both disease activity groups.

Our findings concerning the occurrence of pre-eclampsia and preterm birth support our hypotheses that disease activity of any severity increases the risk of adverse events. A higher risk of pre-eclampsia in women with SLE is well known.[2 7 25] To our knowledge, it has not been demonstrated earlier that women with inactive disease do not have increased risk compared with population controls. The two disease groups were similar concerning risk factors for pre-eclampsia like maternal age, parity, BMI, diabetes, hypertension, prior kidney disease, positive anticardiolipin antibodies and multiple pregnancies. We believe that a threefold higher odds in active versus inactive disease is clinically relevant, even though it did not reach statistical significance. The odds of preterm birth was elevated both in active and inactive diseases compared with population controls, and in active compared with inactive disease. The most vulnerable, very preterm children were also most commonly delivered in women with active disease. In our cohort, we found a lower proportion of women with active kidney disease than reported in other studies.[6 26] Active kidney disease is an important predictor of pre-eclampsia and preterm birth.[22 23 27] Our results showed similar occurrence of these events to other studies,[6 28] which implies that even less serious disease is an important contributor. There was a twofold increase in the odds of pre-eclampsia in women using prednisolone, and a statistically significant threefold increased odds for preterm birth. The assessment of disease activity (LAI-P) includes medication as one of four groups, contributing to the score if medication is increased. However, there was a stable use of medication in our cohort, indicating that it did not influence the score. We therefore do not believe this to be a confounding factor. It is difficult to delineate prednisolone use from active disease as prednisolone is the medication of choice to treat flares in pregnancy. Treatment with prednisolone does in itself indicate more severe disease. However, we cannot exclude the independent effect of prednisolone use. In clinical practice, this finding emphasises the importance of stable disease-modifying treatment with hydroxychloroquine and azathioprine, minimising the need for prednisolone when the disease is not active.

A limitation of this study is a possible selection of patients. Women with more severe disease may choose not to become pregnant, and adverse events can discourage later pregnancies. Another limitation is missing data on disease activity scores. We knew from our recent longitudinal study on disease activity in this patient group that disease activity was not higher in third than in second trimester,[29] and used this registration. The 32 women with missing scores had similar outcomes to the inactive disease group (online supplementary table S4). Since there were lacking data on antiphospholipid antibody status in many patients, we cannot exclude a role for these antibodies concerning our outcomes. Another limitation is that we could not account for dependent observations due to multiple births from the same woman, since this information was unavailable for the population controls. Hence, the precision may be effectively smaller than reported.

Strengths include the utilisation of two nationwide registers. MBRN has existed for more than 40 years. The validity of information on gestational age including birth weight, preterm birth and pregnancy-related hypertensive complications is very good.[30] According to Norwegian guidelines,[31] women with SLE are offered a multidisciplinary follow-up in pregnancy. We therefore believe there are few women who are not followed up closely and included in RevNatus. The tight follow-up through RevNatus contributes to better controlled disease and improved outcomes. Due to the linkage of registers, we could also confirm a good compliance concerning diagnoses. Of 180 women in RevNatus with the diagnosis of SLE, only 10 (5.6%) did not have this diagnosis in MBRN. This is a lower misclassification rate than earlier reported for pre-pregnant rheumatic diseases in MBRN.[32] Furthermore, the diagnosis in RevNatus had to be confirmed by a rheumatologist prior to inclusion, securing the correct diagnosis. An additional strength is the utilisation of a disease activity score validated for use in pregnancy, avoiding pregnancy-related symptoms to be interpreted as active disease. Finally, the birth weight z-score was based on Norwegian standards and gives a more precise estimate for difference in birth weight. However, birth weights in Scandinavian populations cannot be generalised to all ethnic populations.[18]

In conclusion, we found that offspring of women with SLE have lower birth weight than offspring of population controls without rheumatic diseases. Preterm birth is more common in SLE than population controls, and the risk is amplified by active disease. The risk of pre-eclampsia is elevated in active, but not inactive disease. This calls for tight follow-up targeting inactive disease before and throughout pregnancy.

Author affiliations
[1]Department of Neuromedicine and Movement Science (INB), Norwegian University of Science and Technology (NTNU), Trondheim, Norway

[2]Department of Rheumatology, Ålesund Hospital, Ålesund, Norway
[3]Regional Centre for Child and Youth Mental Health and Child Welfare (RKBU), Norwegian University of Science and Technology (NTNU), Trondheim, Norway
[4]Department of Rheumatology, Oslo University Hospital Rikshospitalet, Oslo, Norway
[5]Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases, Department of Rheumatology, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[6]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology (NTNU), Trondheim, Norway
[7]Department of Obstetrics and Gynecology, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

Acknowledgements The authors thank the Medical Birth Registry of Norway (MBRN) for providing data, and the participating departments of rheumatology at the following hospitals for including patients in RevNatus: Betanien Hospital, Skien; Diakonhjemmet Hospital, Oslo; Haugesund Sanitetsforenings Rheumatism Hospital, Haugesund; Haukeland University Hospital, Bergen; Helse Førde, Førde Hospital, Førde; Helse Møre og Romsdal, Ålesund Hospital, Ålesund; Lillehammer Hospital for Rheumatic Diseases, Lillehammer; Nordland Hospital, Bodø; Oslo University Hospital Rikshospitalet, Oslo; Private practice Anne N Bendvold, Kristiansand; St Olavs Hospital, Trondheim University Hospital, Trondheim; Sørlandet Hospital Kristiansand, Kristiansand; University Hospital of North Norway, Tromsø; Vestre Viken Hospital, Drammen; Østfold Hospital, Moss.

Contributors CGS, IMG, JFS, KÅS and MW planned the study. CGS, IMG, ØP, HSSK, BJ and MW provided the data. CGS, SL and MW performed the analysis and drafted the paper. All authors contributed to editing the draft for content and approved the final version. CGS and MW had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Funding The actual work was supported by the Liaison Committee for Education, Research and Innovation in Central Norway.

Competing interests None declared.

Ethics approval RevNatus was approved by the Regional Committee for Medical and Health Research Ethics (REK Mid-Norway). The present study and linking with MBRN was approved by REK Mid-Norway (2012/1905).

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Wallenius M, Salvesen KÅ, Daltveit AK, *et al*. Secular trends of pregnancies in women with inflammatory connective tissue disease. *Acta Obstet Gynecol Scand* 2015;94:1195–202.
2 Simard JF, Arkema EV, Nguyen C, *et al*. Early-onset Preeclampsia in Lupus Pregnancy. *Paediatr Perinat Epidemiol* 2017;31:29–36.
3 Baer AN, Witter FR, Petri M. Lupus and pregnancy. *Obstet Gynecol Surv* 2011;66:639–53.
4 Østensen M, Andreoli L, Brucato A, *et al*. State of the art: Reproduction and pregnancy in rheumatic diseases. *Autoimmun Rev* 2015;14:376–86.
5 Soh MC, Nelson-Piercy C. High-risk pregnancy and the rheumatologist. *Rheumatology* 2015;54:572–87.
6 Buyon JP, Kim MY, Guerra MM, *et al*. Predictors of Pregnancy Outcomes in Patients With Lupus: A Cohort Study. *Ann Intern Med* 2015;163:153–63.
7 Wallenius M, Salvesen KÅ, Daltveit AK, *et al*. Systemic lupus erythematosus and outcomes in first and subsequent births based on data from a national birth registry. *Arthritis Care Res* 2014;66:1718–24.
8 Visentin S, Grumolato F, Nardelli GB, *et al*. Early origins of adult disease: low birth weight and vascular remodeling. *Atherosclerosis* 2014;237:391–9.
9 Lindström L, Skjaerven R, Bergman E, *et al*. Chronic Hypertension in Women after Perinatal Exposure to Preeclampsia, Being Born Small for Gestational Age or Preterm. *Paediatr Perinat Epidemiol* 2017;31:89–98.
10 Soh MC, Nelson-Piercy C, Dib F, *et al*. Brief Report: Association Between Pregnancy Outcomes and Death From Cardiovascular Causes in Parous Women With Systemic Lupus Erythematosus: A Study Using Swedish Population Registries. *Arthritis Rheumatol* 2015;67:2376–82.
11 Gur C, Diav-Citrin O, Shechtman S, *et al*. Pregnancy outcome after first trimester exposure to corticosteroids: a prospective controlled study. *Reprod Toxicol* 2004;18:93–101.
12 Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand* 2000;79:435–9.
13 Staff A, Henriksen T, Langesater E, *et al*. Hypertensive svangerskapskomplikasjoner og eklampsi. http://legeforeningen.no/Fagmed/Norsk-gynekologisk-forening/Veileder/Veileder-i-fodselshjelp-2014/Hypertensive-svangerskapskomplikasjoner-og-eklampsi/
14 Klungsøyr K, Morken NH, Irgens L, *et al*. Secular trends in the epidemiology of pre-eclampsia throughout 40 years in Norway: prevalence, risk factors and perinatal survival. *Paediatr Perinat Epidemiol* 2012;26:190–8.
15 Yu C, Gershwin ME, Chang C. Diagnostic criteria for systemic lupus erythematosus: a critical review. *J Autoimmun* 2014;48-49:10–13.
16 Ruiz-Irastorza G, Khamashta MA. Evaluation of systemic lupus erythematosus activity during pregnancy. *Lupus* 2004;13:679–82.
17 Buyon JP, Kalunian KC, Ramsey-Goldman R, *et al*. Assessing disease activity in SLE patients during pregnancy. *Lupus* 1999;8:677–84.
18 Skjaerven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. *Acta Obstet Gynecol Scand* 2000;79:440–9.
19 Lydersen S, Langaas M, Bakke Øyvind, Bakke O. The exact unconditional *z* -pooled test for equality of two binomial probabilities: optimal choice of the Berger and Boos confidence coefficient. *J Stat Comput Simul* 2012;82:1311–6.
20 Waldenström U, Cnattingius S, Vixner L, *et al*. Advanced maternal age increases the risk of very preterm birth, irrespective of parity: a population-based register study. *BJOG* 2017;124.
21 Wei J, Liu CX, Gong TT, *et al*. Cigarette smoking during pregnancy and preeclampsia risk: a systematic review and meta-analysis of prospective studies. *Oncotarget* 2015;6:43667–78.
22 Smyth A, Oliveira GH, Lahr BD, *et al*. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol* 2010;5:2060–8.
23 Bramham K, Soh MC, Nelson-Piercy C. Pregnancy and renal outcomes in lupus nephritis: an update and guide to management. *Lupus* 2012;21:1271–83.
24 Abou-Nassar K, Carrier M, Ramsay T, *et al*. The association between antiphospholipid antibodies and placenta mediated complications: a systematic review and meta-analysis. *Thromb Res* 2011;128:77–85.
25 Arkema EV, Palmsten K, Sjöwall C, *et al*. What to Expect When Expecting With Systemic Lupus Erythematosus (SLE): A Population-Based Study of Maternal and Fetal Outcomes in SLE and Pre-SLE. *Arthritis Care Res* 2016;68:988–94.
26 Park EJ, Jung H, Hwang J, *et al*. Pregnancy outcomes in patients with systemic lupus erythematosus: a retrospective review of 62 pregnancies at a single tertiary center in South Korea. *Int J Rheum Dis* 2014;17:887–97.
27 Stojan G, Baer AN. Flares of systemic lupus erythematosus during pregnancy and the puerperium: prevention, diagnosis and management. *Expert Rev Clin Immunol* 2012;8:439–53.
28 Clowse ME, Jamison M, Myers E, *et al*. A national study of the complications of lupus in pregnancy. *Am J Obstet Gynecol* 2008;199:127.e1–127.e6.
29 Götestam Skorpen C, Lydersen S, Gilboe IM, *et al*. Disease activity during pregnancy and the First Year postpartum in women with systemic lupus erythematosus. *Arthritis Care Res* 2017;69.
30 Moth FN, Sebastian TR, Horn J, *et al*. Validity of a selection of pregnancy complications in the Medical Birth Registry of Norway. *Acta Obstet Gynecol Scand* 2016;95:519–27.
31 Skomsvoll JF, Wallenius M, Salvesen KA. Inflammatoriske revmatiske sykdommer og kollagenoser. http://legeforeningen.no/Fagmed/Norsk-gynekologisk-forening/Veiledere/Veileder-i-fodselshjelp-2014/Inflammatoriske-revmatiske-sykdommer-og-kollagenoser/
32 Skomsvoll J, Østensen M, Baste V, *et al*. Validity of a rheumatic disease diagnosis in the Medical Birth Registry of Norway. *Acta Obstet Gynecol Scand* 2002;81:831–4.

OPEN ACCESS

EXTENDED REPORT

Stepwise dose increase of febuxostat is comparable with colchicine prophylaxis for the prevention of gout flares during the initial phase of urate-lowering therapy: results from FORTUNE-1, a prospective, multicentre randomised study

Hisashi Yamanaka,[1] Shigenori Tamaki,[2] Yumiko Ide,[3] Hyeteko Kim,[4] Kouichi Inoue,[5] Masayuki Sugimoto,[6] Yuji Hidaka,[7] Atsuo Taniguchi,[1] Shin Fujimori,[8] Tetsuya Yamamoto[9]

Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-211574).

[1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan
[2]Nagoya Rheumatology Clinic, Nagoya, Japan
[3]Tokyo Center Clinic, Tokyo, Japan
[4]Yokohama Minoru Clinic, Yokohama, Japan
[5]Inoue Clinic, Ibaraki, Japan
[6]Shoi-kai Medical Association, Koganeibashi Sakura Clinic, Tokyo, Japan
[7]Taizan-kai Medical Association, Akasaka Central Clinic, Tokyo, Japan
[8]Teikyo University Shinjuku Clinic, Tokyo, Japan
[9]Department of Diabetes, Endocrinology and Metabolism, Hyogo College of Medicine, Hyogo, Japan

Correspondence to
Professor Hisashi Yamanaka, Institute of Rheumatology, Tokyo Women's Medical University 162-0054 10-22 Kawada-cho, Shinjuku-ku, Tokyo, Japan; yamanaka@twmu.ac.jp

Received 31 March 2017
Revised 2 October 2017
Accepted 22 October 2017
Published Online First 8 November 2017

To cite: Yamanaka H, Tamaki S, Ide Y, *et al*. *Ann Rheum Dis* 2018;**77**:270–276.

ABSTRACT

Objectives To determine whether febuxostat with stepwise dose increase is as useful as colchicine prophylaxis in reducing gout flares during the initial introduction of urate-lowering therapy in patients with gout in comparison with febuxostat with no dose titration.

Methods In this prospective, multicentre, randomised open-label comparative study, patients were randomised to group A (stepwise dose increase of febuxostat from 10 to 40 mg/day), group B (fixed-dose febuxostat 40 mg/day plus colchicine 0.5 mg/day) or group C (fixed-dose febuxostat 40 mg/day) and observed for 12 weeks. Gout flare was defined as non-steroidal anti-inflammatory drug use for gout symptoms.

Results A total of 255 patients were randomised, and 241 patients were treated. Among the treated patients, gout flares were experienced by 20/96 (20.8%) in group A, 18/95 (18.9%) in group B and 18/50 (36.0%) in group C. The incidence of flare was significantly lower in groups A and B than that in group C (P=0.047 and P=0.024, respectively), although the differences were not significant after correction for multiple comparisons. No significant difference was noted between the incidence of gout flare in groups A and B.

Conclusions Our data suggested that stepwise dose increase of febuxostat and low-dose colchicine prophylaxis effectively reduced gout flares in comparison with fixed-dose febuxostat alone. Stepwise dose increase of febuxostat may be an effective alternative to low-dose colchicine prophylaxis during the introduction of urate-lowering therapy.

Trial registration number UMIN 000008414.

INTRODUCTION

The number of patients with gout is increasing,[1–3] and the debilitating pain of gout flare can severely impact quality of life. In addition, gout and hyperuricaemia are closely associated with diseases related to metabolic syndrome and renal impairment and may be causally related to cardiovascular disease.[4–6] Gouty arthritis and gouty tophus, clinical presentations of monosodium urate (MSU) crystal deposition, result from persistent hyperuricaemia and can be treated by reducing the body urate pool. This can decrease the long-term incidence of gout flares and urate tophi.[7–11]

However, gout flares frequently develop during the first several months of urate-lowering therapy (ULT).[10–12] The initial serum urate level, the presence of tophus and the dose of urate-lowering drugs can affect the risk of gout flares during ULT. Unfortunately, medication adherence is poor,[13–16] partly because gout flares decrease the motivation of patients to continue treatment.[17 18] The prevention of gout flares is thus of key importance when initiating ULT.

Concomitant colchicine can help[1 19]; recent publications from the European League Against Rheumatism and the American College of Rheumatology recommend colchicine for at least the first 6 months.[1 20] However, although widely used for both therapeutic and prophylactic purposes, colchicine is potentially toxic and caution is advised.[21–23]

ULT induces the shedding of deposited MSU crystals in the joints. Such crystal shedding may be facilitated by the dissolution of urate crystals, and also by decreased urate levels in the joint fluid.[24] Thus, a rapid decrease in serum urate could contribute to gout flares, whereas a gradual decrease should favour flare prevention.[10–12]

In Japan, clinical trials using a stepwise increase in febuxostat dose at the initiation of treatment have shown a lower incidence of gout flares than trials using fixed-dose febuxostat.[25 26] Thus, there are at least two potential strategies to reduce early treatment-related gout flares: stepwise dose increase and colchicine prophylaxis. However, no prospective clinical trials have been conducted to compare the efficacy of these two strategies.

The present study was designed to investigate the incidence of gout flares during early-stage febuxostat treatment, comparing fixed-dose monotherapy both to stepwise dose increase and to low-dose colchicine prophylaxis.

PATIENTS AND METHODS

Patients

Men with gout who had at least one episode of gouty arthritis within 1 year before study entry, whose serum urate exceeded 7.0 mg/dL (416.39 µmol/L) and who had not received treatment with any urate-lowering drugs for at least 1 month prior to entry were enrolled after giving written informed consent. Diagnosis of gout was based on the 1977 criteria.[27] Patients experiencing gouty arthritis within 2 weeks before study entry were excluded. Other exclusion criteria were age <20 years, history of allergic reaction to febuxostat, colchicine or non-steroidal anti-inflammatory drugs (NSAIDs), presence of serious comorbidities including serum creatinine level of 2.0 mg/dL or higher and the judgement of the investigator that the patient was not an appropriate candidate for study participation. Inclusion and exclusion criteria are detailed in online supplementary table 1.

Study design

This prospective, multicentre, randomised, open-label comparative study was conducted by the Febuxostat Outcome Research Towards Urate Lowering in the Next Decade (FORTUNE) consortium, organised by multiple clinical sites across Japan,[28] and was designated the FORTUNE-1 study. Patients were randomised as follows: group A, stepwise dose increase of febuxostat from 10 mg/day (4 weeks), 20 mg/day (4 weeks) and 40 mg/day (until the end of the study); group B, febuxostat 40 mg/day from the start of the study, with concomitant colchicine 0.5 mg/day; or group C, febuxostat 40 mg/day from the start of the study. Patients took oral febuxostat one time per day in the morning, or oral febuxostat and colchicine at the same time one time per day in the morning.

This randomised treatment was conducted during the first 12 weeks (randomised period), after which all patients were treated with febuxostat 40 mg/day for another 12 weeks (observation period).

Because we anticipated that the incidence of gout flares might be higher in group C, the randomisation ratio for groups A, B and C was set at 2:2:1 for ethical reasons.

The allocation sequence was computer generated by a data centre (Mebix, Tokyo), using a random number table. Randomisation was by minimisation,[29] adjusted by baseline serum urate (<8.0 mg/dL (475.88 µmol/L) or ≥8.0 mg/dL (475.88 µmol/L)), age (<50 or ≥50 years), previous anti-hyperuricaemic therapy (<1 or ≥1) and previous incidence of gouty flare (1 or ≥2 per year). The investigators initiated treatment after being informed of the results of assignment by the data centre.

This study used an open-label design; investigators and patients were aware of their treatment arm. Investigators handled patient assessment and data collection.

The attending investigator evaluated each adverse event (AE) and graded the severity as mild (awareness of sign or symptom but no significant discomfort), moderate (discomfort requiring intervention) or severe (prevents daily routine activity or has a clinically important effect). If a causal relationship with febuxostat could not be ruled out, attending physicians could reduce the dose or discontinue febuxostat. During the study, other urate-lowering drugs and drugs that are known to increase or decrease the serum urate level were prohibited. Attending physicians were requested to prescribe NSAIDs at the start of the study for use in managing gout flares. Patients who did not therapeutically respond to NSAIDs or had multiple flares were given corticosteroids.

Sample size

The sample size for the study was based on the primary end point. A previous study noted that a lower percentage of patients experienced gout flares in groups A and B than that in group C.[30] Based on earlier reports in the literature,[25 26 30] we estimated that the incidence of gout flares during a 12-week treatment period would be 5% for groups A and B and 25% for group C in this study. Thus, for ethical reasons, we set the ratio of treatment groups at 2:2:1. To achieve a 5% two-sided significance level and 89% power to detect the differences between group A and group C and between group B and group C, we calculated that 90 patients were required for group A, 90 patients for group B and 45 patients for group C. We estimated a 10% dropout rate from the study and, thus, set the sample size to 100, 100 and 50 patients, respectively.

End points

The primary end point was the incidence rate of gouty arthritis (gouty aura not included) during the 'treatment period' (the first 12 weeks of the study), defined as the percentage of patients who needed analgesic treatment with NSAIDs or adrenal corticosteroid to manage gout symptoms.

Patients were instructed to record symptoms and NSAID use in the specified patient record form. Rubor, swelling and other symptoms were verified by the attending investigator during the patient's next visit. Visits occurred every 4 weeks. Mild attacks that were tolerable without NSAID use were not defined as gout flares. Any use of NSAIDs for reasons other than gouty arthritis was excluded from analysis.

The secondary end points included the number of gout flares per patient during the first 12 weeks (randomised period), the number of gout flares per patient during the second 12 weeks (observation period) and the percentage of patients with serum urate ≤6.0 mg/dL (356.91 µmol/L) in the second 12 weeks (observation period).

An AE was defined as any untoward medical occurrence in a subject given the study drug, without requiring a causal relationship to the treatment. An adverse reaction (AR) was defined as any event for which a causal relationship to febuxostat could not be ruled out.

Statistical analysis

All statistical analyses were performed on the full analysis set (FAS) as defined in the Results section. Baseline patient demographics were presented as mean and SD for continuous variables and as frequency for categorical variables. In the primary end point analysis, the statistical analysis was corrected for multiple comparisons. A Pearson χ^2 test on a 3×2 table was used to compare group A with group C. The higher of the two P values was used to test for significance using a threshold of 0.05. This preserves the family-wise error rate when only three groups are involved.[31]

For secondary end point analyses, corrections for multiple testing were not performed.

The Wilcoxon rank-sum test was used for the number of gout flares, and the Fisher exact test was used for the percentage of patients with serum urate ≤6.0 mg/dL (356.91 µmol/L).

All tests were two-sided. Statistical significance was at P<0.05. Baseline demographics were summarised using SAS V.9.4 (SAS Institute). Other analyses were performed using R V.3.0.3.[32]

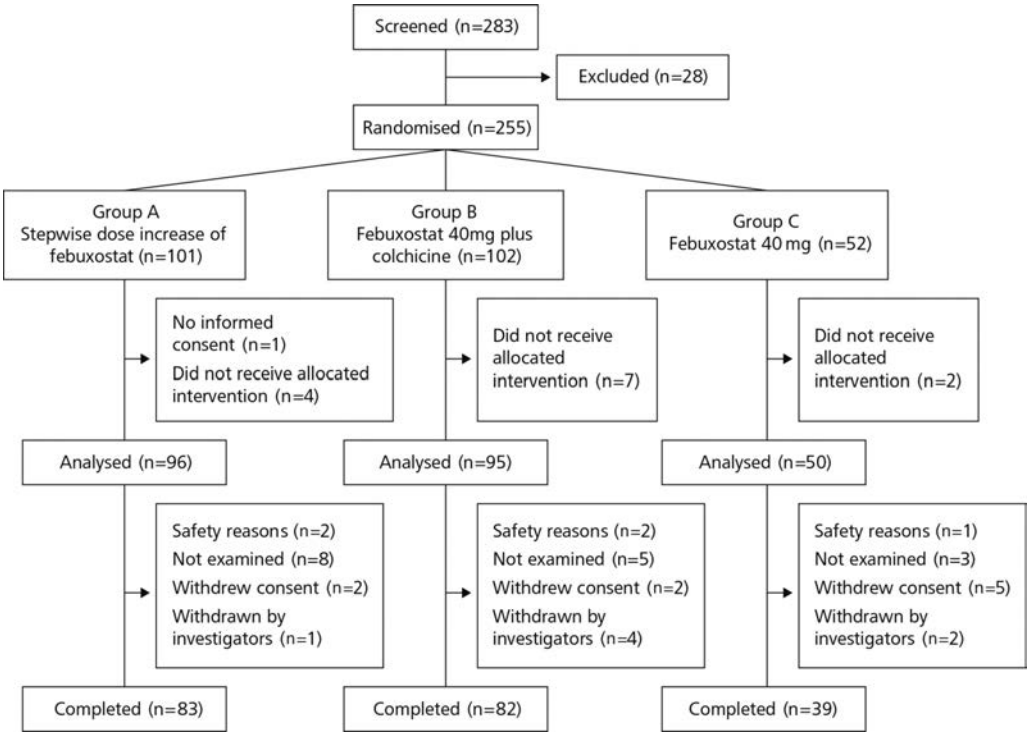


Figure 1 Patient disposition.

RESULTS

Patient disposition and baseline characteristics

The trial was conducted at 24 centres between August 2013 and February 2015. As shown in figure 1, a total of 283 patients agreed to participate in this study (intention-to-treat group). After excluding patients who met the exclusion criteria or did not meet the inclusion criteria, we randomised 255 patients (group A, 101; group B, 102; group C, 52) for the study. Patients received treatment for 12 weeks and were monitored for an additional 12 weeks. A total of 14 patients were excluded from primary end point analysis: 13 patients because treatment was declined by the doctor or the patient and 1 patient without informed consent. The remaining 241 patients were defined as the FAS. The data from these 241 patients (group A, 96; group B, 95; group C, 50) were used for subsequent analyses (figure 1).

Table 1 summarises the baseline characteristics of these 241 patients. One-third of the patients had received prior ULT; urate-lowering drugs were washed out for more than 1 month in these patients. No statistically significant differences were noted in the baseline features of the three groups.

Incidence of gout flares in the first 12 weeks (randomised period)

Gout flares were experienced within the first 12 weeks (randomised period) by 20 of 96 (20.8%) patients in group A, 18 of 95 patients (18.9%) in group B and 18 of 50 patients (36.0%) in group C (figure 2). In an overall Pearson χ^2 test, the P value was 0.054, and for the comparison of groups A and C, the P value was 0.048. Although this P value was below 0.05, the null hypothesis for the primary end point was not rejected because the higher P value of the two tests (0.054) was above the 0.05 threshold. The difference in flare incidence was statistically significant between group B and group C (P=0.024)

Table 1 Baseline demographics of patients (FAS)

	Group A (n=96)	Group B (n=95)	Group C (n=50)
	Febuxostat dose increasing 10–40 mg	Febuxostat 40 mg+colchicine	Febuxostat 40 mg
Age, mean (SD)	47.4 (10.5)	47.6 (11.1)	46.4 (12.7)
Height, mean (SD), cm	171.0 (5.7)	170.8 (5.8)	169.8 (6.9)
Weight, mean (SD), kg	77.3 (12.4)	76.5 (11.7)	76.8 (16.4)
BMI, mean (SD), kg/m^2	26.4 (3.6)	26.2 (3.5)	26.5 (5.1)
Systolic blood pressure, mean (SD), mm Hg	132.6 (14.4)	132.8 (16.3)	132.6 (17.6)
Diastolic blood pressure, mean (SD), mm Hg	84.5 (12.0)	84.3 (11.9)	82.6 (14.0)
Any history of ≥2 gout flares, n (%)	74 (77.1)	70 (73.7)	38 (76.0)
Prior urate-lowering therapy, n (%)	31 (32.3)	31 (32.6)	16 (32.0)
eGFR at entry, mean (SD), mL/min/1.73 m^2	75.8 (16.2)	76.6 (13.7)	76.8 (17.5)
Serum urate at entry, mean (SD), mg/dL	8.67 (1.38)	8.51 (1.19)	8.57 (1.17)
Serum creatinine at entry, mean (SD), mg/dL	0.90 (0.16)	0.88 (0.14)	0.89 (0.15)
With any comorbidity, n (%)	51 (53.1)	47 (49.5)	29 (58.0)

BMI, body mass index; eGFR, estimated glomerular filtration rate; FAS, full analysis set.

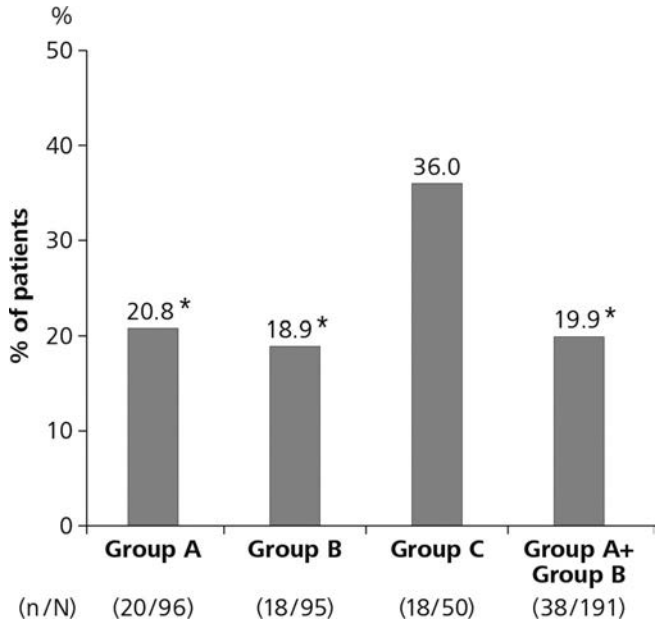


Figure 2 Incidence of gout flares during the randomised period. Incidence of gout flares during the first 12 weeks (randomised period) in group A (stepwise dose increase of febuxostat from 10 to 40 mg/day), group B (febuxostat 40 mg/day plus colchicine 0.5 mg/day) and group C (febuxostat 40 mg/day). The overall Pearson χ^2 test was not significant. See text for details. *P<0.05 vs group C.

and between group A+group B and group C (19.9%, 95% CI 14.2 to 25.6, P=0.016) but not between group A and group B (P=0.744).

The incidence of gout flare was compared in patients previously treated with ULT and those who were treatment naïve at baseline. There was no significant difference in the incidence of gout flares in patients with or without previous ULT within each treatment group or within the entire study group (online supplementary table 2).

Number of gout flares per patient in the study period

To investigate the characteristic time course of gout flares in each group, we analysed the number of gout flares in each study period.

During the first 12 weeks (randomised period), a total of 27 flares were identified in 20 patients (1.35 flares/patient) in group A, 24 flares in 18 patients (1.33 flares/patient) in group B and 37 flares in 18 patients (2.06 flares/patient) in group C. There was no significant difference between group A and group C or between group B and group C. In the second 12 weeks (observation period), there were 18 flares in 15 patients (1.20 flares/patient) in group A, 26 flares in 17 patients (1.53 flares/patient) in group B and 8 flares in six patients (1.33 flares/patient) in group C. There was no significant difference between treatment groups. The number of flares in each patient who had gout flares in the first 12 weeks and the second 12 weeks is illustrated in figure 3A,B, respectively.

During the 24 weeks (randomised + observational periods), there were 45 flares in 30 patients (1.50 flares/patient) in group A, 59 flares in 28 patients (1.79 flares/patient) in group B and 45 flares in 19 patients (2.37 flares/patient) in group C. The number of flares in each patient is illustrated in online supplementary figure 1.

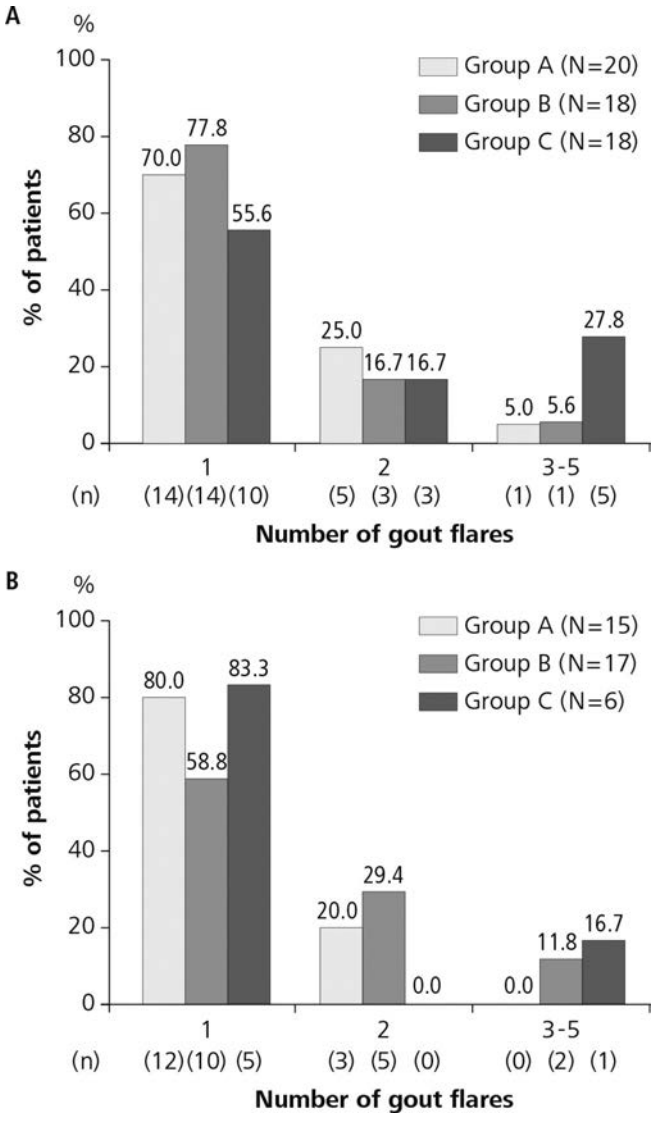


Figure 3 Number of gout flares during the study period. Number of gout flares per patient during the first 12 weeks (randomised period) (A) and the second 12 weeks (observation period) (B). Group A (stepwise dose increase of febuxostat from 10 to 40 mg/day), group B (febuxostat 40 mg/day plus colchicine 0.5 mg/day) and group C (febuxostat 40 mg/day).

Percentage of patients with serum urate ≤6.0 mg/dL (356.91 µmol/L)

Urate-lowering effects of treatment were investigated in the 241 patients. Some data were missing because treatment had been discontinued or were otherwise unavailable. Figure 4 shows the percentage of patients whose serum urate decreased to 6.0 mg/dL (356.91 µmol/L) or below at weeks 4, 8, 12, 16, 20 and 24, and the number of patients used for calculations for each time point and each group.

A significantly lower percentage of patients reached the target level of serum urate at 4 weeks (P<0.001) and 8 weeks (P<0.001) in group A compared with group B or group C. There was no significant difference among the three treatment groups after 12 weeks.

Safety profile

AEs and ARs are listed in table 2. No clinically important AEs or serious AEs were reported. No differences were identified in the

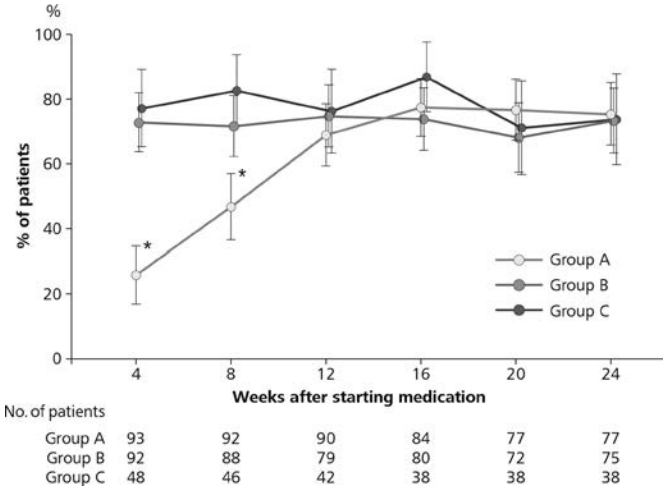


Figure 4 Percentage of patients with serum urate level ≤6.0 mg/dL (356.91 µmol/L) in the three randomised groups. Group A (stepwise dose increase of febuxostat from 10 to 40 mg/day), group B (febuxostat 40 mg/day plus colchicine 0.5 mg/day) and group C (febuxostat 40 mg/day). The number of patients for calculations based on urate data at each weekly time point in each group is shown below the figure. *P<0.001 vs group B or group C.

incidence of ARs among the three groups. Moderate diarrhoea was reported in one patient in group B, but not in any patients in group A or group C.

DISCUSSION

Febuxostat is a xanthine oxidase inhibitor with a potent serum urate-lowering effect and a reliable safety profile.[25 26 33] In the first clinical studies of febuxostat in Japan, gout flare was the major AE; subsequent study designs incorporated a stepwise dose increase, which reduced the incidence of gout flares.[25 26] As a result, the official labelling for Feburic (commercial name of febuxostat in Japan) specifies a stepwise increase in the febuxostat dose.

There are two possible ways to reduce gout flares during the initial period of ULT: colchicine prophylaxis and stepwise dose increase. Our study is the first to compare these two strategies, using febuxostat as the urate-lowering drug. As a control, febuxostat 40 mg without colchicine prophylaxis and without stepwise dose increase (group C) was included. For ethical reasons (to minimise the disadvantage to patients), fewer patients were randomised to this arm, and all patients were instructed to take an NSAID if a flare should occur.

The result of the primary end point analysis that included the correction for multiple comparisons was negative. However, as shown in figure 2, the incidence of gout flares was significantly lower in group A (stepwise dose increase) than that in group C (without stepwise dose increase or colchicine prophylaxis) and was also significantly lower in group B (low-dose colchicine prophylaxis) than that in group C. These findings were further confirmed by comparing incidence of flares between groups A plus B and group C.

We found no difference in the incidence or the number of gout flares between group A and group B. This suggests that,

Table 2 Incidence of adverse events and adverse reactions by system organ class (safety population)

	Total (n=241)	Group A (n=96)	Group B (n=95)	Group C (n=50)
		Febuxostat dose increasing stepwise from 10 to 40 mg	Febuxostat 40mg+colchicine	Febuxostat 40 mg
	Patients (events) %	Patients (events) %	Patients (events) %	Patients (events) %
Adverse events	51 (74) 21.2	21 (35) 21.9	19 (23) 20.0	11 (16) 22.0
Infections and infestations	25 (35) 10.4	9 (15) 9.4	11 (13) 11.6	5 (7) 10.0
Neoplasms benign, malignant and unspecified	1 (1) 0.4	1 (1) 1.0	–	–
Metabolism and nutrition disorders	2 (2) 0.8	2 (2) 2.1	–	–
Vascular disorders	1 (1) 0.4	1 (1) 1.0	–	–
Respiratory, thoracic and mediastinal disorders	4 (6) 1.7	2 (4) 2.1	1 (1) 1.1	1 (1) 2.0
Gastrointestinal disorders	1 (1) 0.4	–	1 (1) 1.1	–
Hepatobiliary disorders	5 (5) 2.1	4 (4) 4.2	–	1 (1) 2.0
Skin and subcutaneous tissue disorders	2 (2) 0.8	1 (1) 1.0	1 (1) 1.1	–
Musculoskeletal and connective tissue disorders	9 (10) 3.7	4 (5) 4.2	3 (3) 3.2	2 (2) 4.0
Renal and urinary disorders	2 (2) 0.8	1 (1) 1.0	1 (1) 1.1	–
Investigations	4 (4) 1.7	–	3 (3) 3.2	1 (1) 2.0
Injury, poisoning and procedural complications	4 (4) 1.7	1 (1) 1.0	–	3 (3) 6.0
Surgical and medical procedures	1 (1) 0.4	–	–	1 (1) 2.0
Adverse reactions	21 (24) 8.7	7 (9) 7.3	9 (10) 9.5	5 (5) 10.0
Infections and infestations	7 (8) 2.9	–	6 (7) 6.3	1 (1) 2.0
Metabolism and nutrition disorders	1 (1) 0.4	1 (1) 1.0	–	–
Respiratory, thoracic and mediastinal disorders	1 (1) 0.4	–	1 (1) 1.1	–
Hepatobiliary disorders	4 (4) 1.7	3 (3) 3.1	–	1 (1) 2.0
Skin and subcutaneous tissue disorders	2 (2) 0.8	1 (1) 1.0	1 (1) 1.1	–
Musculoskeletal and connective tissue disorders	3 (4) 1.2	2 (3) 2.1	–	1 (1) 2.0
Renal and urinary disorders	2 (2) 0.8	1 (1) 1.0	1 (1) 1.1	–
Investigations	1 (1) 0.4	–	–	1 (1) 2.0
Injury, poisoning and procedural complications	1 (1) 0.4	–	–	1 (1) 2.0

Number of events, tabulated by system organ class (SOC, MedDRA 17.1).

when introducing ULT with febuxostat, stepwise dose increase of febuxostat is better than the single-dose method and is comparable with low-dose colchicine prophylaxis for the prevention of gout flares. Because colchicine prophylaxis has been shown to decrease gout flares during the introduction of allopurinol,[34] stepwise dose increase of febuxostat is also likely to be beneficial for gout patients.

Non-inferiority or equivalence testing of gout flares between group A and group B would confirm whether febuxostat stepwise dose increase is comparable with colchicine prophylaxis in reducing gout flares. However, such tests were not performed in the present study because of insufficient sample size. Under the current concept of treat to target, the recommended serum urate level is to be maintained below 6.0 mg/dL (356.91 µmol/L).[35 36] Under stepwise dose increase, lowering of urate to the target level (6.0 mg/dL (356.91 µmol/L)) was delayed in group A, but by week 12, the same percentage of patients had achieved serum urate at or below 6.0 mg/dL (356.91 µmol/L) as in the other two groups. This suggests that stepwise dose increase is a practical treatment option. This is particularly important because colchicine can be toxic in large amounts,[21 37] suggesting that the use of colchicine should potentially be restricted in patients with multiple comorbidities. Thus, we propose stepwise dose increase of febuxostat as a useful alternative option to minimise the occurrence of gout flares when starting ULT.

Limitations of this study include the open-label design (patients and investigators were informed of the patient's treatment arm, which might have affected study results) and the definition of gout flare (under discussion in the literature[38]; the provisional definition[39] may not apply in studies of real-world clinical therapy). For this study, we defined gout flares as symptoms of gout requiring NSAID treatment. This definition is not universally accepted,[37 38] but we consider it reasonably useful for comparing the incidence of gout flares among three treatment arms in our study. The severity of gout may also be a consideration. Japanese patients generally have milder forms of gout than patients in the USA or Europe, as measured by the percentage of patients with tophi[25 26] or the dose of febuxostat required.[40] The usual dose of febuxostat for lowering serum urate to below 6.0 mg/dL (356.91 µmol/L) is 40 mg/day in Japan and 80 mg/day in the USA or Europe, perhaps due to smaller body size and earlier intervention for hyperuricaemia in Japan. Also, the dose of colchicine for gout flare prophylaxis in group B was consistent with Japanese labelling for colchicine but lower than that in other countries. Thus, the results of this study may not be directly applicable to patients with gout in the USA or Europe. Finally, this study may have failed to meet the primary end point because of insufficient sample size, especially in group C. This should influence the design of future studies.

In conclusion, our results suggested that a stepwise dose increase of febuxostat reduced the incidence of gout flares to an extent comparable with low-dose colchicine prophylaxis. Because of issues related to the safety of colchicine, a stepwise dose increase of febuxostat can be a recommended option for reducing the incidence of gout flares. We hope that this strategy can increase patient adherence and improve long-term outcomes.

Correction notice This article has been corrected since it published Online First. The corresponding author's email address has been corrected.

Acknowledgements The authors thank the contract research organisation Mebix Corporation (http://www.mebix.co.jp) for data collection and the Nature Insight Corporation (http://www.n-insight.co.jp/) and StaGen (www.stagen.co.jp) for statistical analysis, especially the very helpful explanations from Dr Naoyuki Kamatani and Dr Eisuke Inoue. We also thank Dr Naoyuki Kamatani for his useful comments on the study.

Collaborators The institutions and names of the chief investigators of the FORTUNE-1 study group are listed below: 1. Institute of Rheumatology, Tokyo Women's Medical University, Hisashi Yamanaka (principal investigator); 2. Nagoya Rheumatology Clinic, Shigenori Tamaki; 3. Tokyo Center Clinic, Yumiko Ide; 4. Yokohama Minoru Clinic, Hyeteko Kim; 5. Inoue Clinic, Kouichi Inoue; 6. Syoi-kai Medical Association Koganeibashi Sakura Clinic, Masayuki Sugimoto; 7. Taizan-kai Medical Association Akasaka Central Clinic, Yuji Hidaka; 8. Taizan-kai Medical Association Toranomon Clinic, Mitsuko Akimoto; 9. Institute of Rheumatology, Tokyo Women's Medical University, Naomi Ichikawa; 10. Sagawa Akira Rheumatology Clinic, Akira Sagawa; 11. Isei-kai Medical Association Sakaibashi Clinic, Hisayoshi Hirota; 12. Jyakuei-kai Medical Association Tanaka Hospital, Tsuneo Tanaka; 13. Kowa-kai Medical Association Jin Orthopedics Clinic, Hiroaki Jin; 14. Koni Clinic, Ichiro Koni; 15. Seiga-kai Medical Association Momoi Orthopedics Clinic, Yasuharu Momoi; 16. Inoue Orthopedics Clinic, Soitiro Inoue; 17. East Sendai Rheumatism and Internal Medicine Clinic, Tomomasa Izumiyama; 18. Seisyu-kai Medical Association Yagi Clinic, Hideyuki Yagi; 19. National Hospital Organization Awara Hospital, Hiroshi Tsutani; 20. Senoo Hospital, Masayuki Hakoda; 21. Tohoku University Hospital, Tomonori Ishii; 22. Nakashima Hiroshi Clinic,Hiroshi Nakashima; 23. Chiba Prefectural Togane Hospital, Aizan Hirai.

Contributors All authors have equal responsibility for the manuscript and meet all the authorship requirements. The corresponding author (HY) organised every stage of the study, including the naming of the study, and was responsible for drafting the manuscript. HY, AT, SF and TY participated in the design of the study and helped to revise the manuscript. All authors were members of the FORTUNE-1 study group, participated in data acquisition and gave suggestions as necessary; those suggestions provided the basis for modifications to the manuscript. All authors have read and approved this revised version of the manuscript for submission. The corresponding author had full responsibility for the study design, supervised the data collection, had full access to all data, supervised data analysis and was responsible for submitting the manuscript for publication.

Funding This investigator-initiated study was supported by a grant from Teijin Pharma Limited. The sponsors were not involved in the design of the study; enrolment of patients; data collection, analysis and interpretation; or preparation of the manuscript.

Competing interests HY reports grants and personal fees from Teijin Pharma, Pfizer Japan, Takeda Pharmaceutical Company, Bristol-Myers Squibb, Nippon Kayaku, Chugai Pharmaceutical, Mitsubishi Tanabe Pharma, Daiichi Sankyo, Astellas Pharma, AbbVie, UCB Japan, Ono Pharmaceutical, Ayumi Pharmaceutical, Eisai, Torii Pharmaceutical, Taisho Toyama Pharmaceutical and YL Biologics, and grants from MSD. ST reports personal fees from Teijin Pharma. YH reports personal fees from Teijin Pharma, Pfizer Japan, Sanwa Kagaku Kenkyusho and Fujiyakuhin. AT reports personal fees from Teijin Pharma. SF reports personal fees from Teijin Pharma, Sanwa Kagaku Kenkyusho, Fujiyakuhin, Astellas Pharma, Kissei Pharmaceutical, Pfizer Japan, MSD and Nippon Chemiphar. TY reports personal fees and non-financial support from Teijin Pharma.

Patient consent Obtained.

Ethics approval The study was approved by the ethics committee of each investigator's institute or hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Richette P, Doherty M, Pascual E, *et al*. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis* 2017;76:29–42.
2 Kuo CF, Grainge MJ, Zhang W, *et al*. Global epidemiology of gout: prevalence, incidence and risk factors. *Nat Rev Rheumatol* 2015;11:649–62.
3 Kuo CF, Grainge MJ, Mallen C, *et al*. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis* 2015;74:661–7.
4 Abeles AM. Hyperuricemia, gout, and cardiovascular disease: an update. *Curr Rheumatol Rep* 2015;17:13.
5 Kuo CF, Grainge MJ, Mallen C, *et al*. Comorbidities in patients with gout prior to and following diagnosis: case-control study. *Ann Rheum Dis* 2016;75:210–7.
6 Perez-Ruiz F, Becker MA. Inflammation: a possible mechanism for a causative role of hyperuricemia/gout in cardiovascular disease. *Curr Med Res Opin* 2015;31(Suppl 2):9–14.

7 Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. *Arthritis Rheum* 2004;51:321–5.
8 Perez-Ruiz F, Calabozo M, Pijoan JI, *et al*. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Rheum* 2002;47:356–60.
9 Schumacher HR Jr, Becker MA, Lloyd E, *et al*. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study. *Rheumatology* 2009;48 :188–94.
10 Schumacher HR Jr, Becker MA, Wortmann RL, *et al*. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum* 2008;59:1540–8.
11 Sundy JS, Baraf HS, Yood RA, *et al*. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. *JAMA* 2011;306:711–20.
12 Becker MA, Schumacher HR Jr, Wortmann RL, *et al*. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med* 2005;353:2450–61.
13 Lee S, So MW. Adherence with urate-lowering therapies among male patients with gout in a routine clinical setting. *Mod Rheumatol* 2016;26:950–5.
14 McGowan B, Bennett K, Silke C, *et al*. Adherence and persistence to urate-lowering therapies in the Irish setting. *Clin Rheumatol* 2016;35:715–21.
15 Becker MA, MacDonald PA, Hunt BJ, *et al*. Determinants of the clinical outcomes of gout during the first year of urate-lowering therapy. *Nucleosides Nucleotides Nucleic Acids* 2008;27:585–91.
16 Briesacher BA, Andrade SE, Fouayzi H, *et al*. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy* 2008;28:437–43.
17 Riedel AA, Nelson M, Joseph-Ridge N, *et al*. Compliance with allopurinol therapy among managed care enrollees with gout: a retrospective analysis of administrative claims. *J Rheumatol* 2004;31:1575–81.
18 Zandman-Goddard G, Amital H, Shamrayevsky N, *et al*. Rates of adherence and persistence with allopurinol therapy among gout patients in Israel. *Rheumatology* 2013;52:1126–31.
19 Seth R, Kydd AS, Falzon L, *et al*. Preventing attacks of acute gout when introducing urate-lowering therapy: a systematic literature review. *J Rheumatol Suppl* 2014;92:42–7.
20 Khanna D, Khanna PP, Fitzgerald JD, *et al*. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res* 2012;64:1447–61.
21 van Echteld I, Wechalekar MD, Schlesinger N, *et al*. Colchicine for acute gout. *Cochrane Database Syst Rev* 2014;8:CD006190.
22 Terkeltaub RA, Furst DE, Bennett K, *et al*. High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum* 2010;62:1060–8.
23 Finkelstein Y, Aks SE, Hutson JR, *et al*. Colchicine poisoning: the dark side of an ancient drug. *Clin Toxicol* 2010;48:407–14.
24 Schlesinger N. Treatment of chronic gouty arthritis: it is not just about urate-lowering therapy. *Semin Arthritis Rheum* 2012;42:155–65.
25 Kamatani N, Fujimori S, Hada T, *et al*. Placebo-controlled double-blind dose-response study of the non-purine-selective xanthine oxidase inhibitor febuxostat (TMX-67) in patients with hyperuricemia (including gout patients) in Japan: late phase 2 clinical study. *J Clin Rheumatol* 2011;17:S35–43.
26 Kamatani N, Fujimori S, Hada T, *et al*. An allopurinol-controlled, randomised, double-dummy, double-blind, parallel between-group, comparative study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with hyperuricemia including those with gout in Japan: phase 3 clinical study. *J Clin Rheumatol* 2011;17:S13–S18.
27 Wallace SL, Robinson H, Masi AT, *et al*. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum* 1977;20:895–900.
28 Yamamoto T, Hidaka Y, Inaba M, *et al*. Effects of febuxostat on serum urate level in Japanese hyperuricemia patients. *Mod Rheumatol* 2015;25:779–83.
29 Pocock SJ. *Clinical Trials: A Practical Approach*. New York: John Wiley & Sons, 1983.
30 Kamatani N, Fujimori S, Hada T, *et al*. Placebo-controlled, double-blind study of the non-purine-selective xanthine oxidase inhibitor febuxostat (TMX-67) in patients with hyperuricemia including those with gout in Japan: phase 3 clinical study. *J Clin Rheumatol* 2011;17:S19–26.
31 Bender R, Lange S. Adjusting for multiple testing--when and how? *J Clin Epidemiol* 2001;54:343–9.
32 R Core Team. *R: A language and environment for statistical computing. R Foundation for Statistical Computing*. Vienna, Austria, 2014. http://www.R-project.org/
33 Komoriya K, Hoshide S, Takeda K, *et al*. Pharmacokinetics and pharmacodynamics of febuxostat (TMX-67), a non-purine selective inhibitor of xanthine oxidase/xanthine dehydrogenase (NPSIXO) in patients with gout and/or hyperuricemia. *Nucleosides Nucleotides Nucleic Acids* 2004;23:1119–22.
34 Borstad GC, Bryant LR, Abel MP, *et al*. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. *J Rheumatol* 2004;31:2429–32.
35 Khanna D, Fitzgerald JD, Khanna PP, *et al*. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res* 2012;64:1431–46.
36 Perez-Ruiz F. Treating to target: a strategy to cure gout. *Rheumatology* 2009;48:ii9–ii14.
37 Stamp LK. Safety profile of anti-gout agents: an update. *Curr Opin Rheumatol* 2014;26:162–8.
38 Taylor WJ, Shewchuk R, Saag KG, *et al*. Toward a valid definition of gout flare: results of consensus exercises using Delphi methodology and cognitive mapping. *Arthritis Rheum* 2009;61:535–43.
39 Gaffo AL, Schumacher HR, Saag KG, *et al*. Developing a provisional definition of flare in patients with established gout. *Arthritis Rheum* 2012;64:1508–17.
40 Saag KG, Whelton A, Becker MA, *et al*. Impact of febuxostat on renal function in gout subjects with moderate-to-severe renal impairment. *Arthritis Rheum* 2016;68:2035–43.

CONCISE REPORT

Risk of uveitis and inflammatory bowel disease in people with psoriatic arthritis: a population-based cohort study

Rachel Charlton,[1] Amelia Green,[1,2] Gavin Shaddick,[3] Julia Snowball,[1] Alison Nightingale,[1] William Tillett,[1,4] Catherine H Smith,[5] Neil McHugh,[1,4] on behalf of the PROMPT study group

Handling editor Josef S Smolen

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-212328).

[1]Department of Pharmacy and Pharmacology, University of Bath, Bath, UK
[2]Department of Mathematical Sciences, University of Bath, Bath, UK
[3]Department of Mathematics, University of Exeter, Exeter, Devon, UK
[4]Department of Rheumatology, Royal National Hospital for Rheumatic Diseases, Bath, UK
[5]Guy's and St Thomas' Foundation Trust, St John's Institute of Dermatology, London, UK

Correspondence to
Dr Rachel Charlton, Department of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA27AY, UK; r.a.charlton@bath.ac.uk

The initial findings of the study presented in this manuscript were presented as a poster presentation at the British Society for Rheumatology Conference 2017. Rheumatology, volume 56, Issue Suppl_2, 1 April 2017, kex062.048, https://doi.org/10.1093/rheumatology/kex062.048.

Received 1 September 2017
Revised 2 October 2017
Accepted 22 October 2017
Published Online First 1 November 2017

To cite: Charlton R, Green A, Shaddick G, *et al*. *Ann Rheum Dis* 2018;**77**:277–280.

ABSTRACT

Objectives To determine the risk of uveitis and inflammatory bowel disease (IBD) in patients with psoriatic arthritis (PsA) compared with the general population and patients with psoriasis.

Methods A cohort study using data from the UK Clinical Practice Research Datalink between 1998 and 2014. Patients with incident PsA aged 18–89 years were identified and matched to a cohort of patients with psoriasis and a general population cohort. The incidence of uveitis, all IBD, Crohn's disease and ulcerative colitis was calculated for each study cohort and adjusted relative risks (RR_{adj}) were calculated using conditional Poisson regression.

Results 6783 incident cases of PsA were identified with a median age of 49 years. The risk of uveitis was significantly higher in the PsA cohort than in the general population and psoriasis cohorts (RR_{adj} 3.55, 95% CI 2.21 to 5.70 and RR_{adj} 2.13, 95% CI 1.40 to 3.24, respectively). A significant increase was observed for Crohn's disease (RR_{adj} 2.96, 95% CI 1.46 to 6.00 and RR_{adj} 3.60, 95% CI 1.83 to 7.10) but not for ulcerative colitis (RR_{adj} 1.30, 95% CI 0.66 to 2.56 and RR_{adj} 0.98, 95% CI 0.50 to 1.92).

Conclusions In a primary care-based incidence cohort of patients with PsA, there were substantial risks of developing uveitis and/or Crohn's disease, but not ulcerative colitis, when compared with the general population and psoriasis controls.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis which has been reported to affect between 10% and 40% of individuals with psoriasis.[1] In the majority of patients, PsA presents after, or synchronously with, the onset of psoriasis. PsA is well recognised to be progressive and may result in severe disability, reduced quality of life and work disability.[2 3] Patients with PsA can often suffer from multiple comorbidities, resulting in increased morbidity and mortality.

Uveitis and inflammatory bowel disease (IBD) are known to be associated with spondyloarthritis[4]; however, there is limited information on the prevalence and incidence of these conditions in patients with PsA and current estimates and study designs vary. Recent Danish and Taiwanese nationwide cohort studies, using administrative data, have reported an increased risk of uveitis associated with psoriatic disease.[5 6] The Danish study demonstrated a bidirectional association, with patients with psoriasis and PsA having an increased risk of uveitis and patients with uveitis having an increased risk of psoriasis and PsA, suggesting a shared pathogenic pathway.[5] Another study, using the same Danish data source, has reported an increased risk of Crohn's disease and ulcerative colitis among patients with psoriasis and PsA,[7] as have two studies using data from US Health Claims databases,[8 9] and one looking at PsA using data from an Israeli healthcare database.[10] A further study analysing data on 174 476 women participating in a US Nurses' Health Study, however, reported an increased risk of Crohn's disease in patients with psoriasis and/or PsA but not an increased risk of ulcerative colitis.[11]

This study aimed to determine the risks of uveitis and IBD in patients with PsA in the UK and compare these with the risks in a matched cohort of patients with psoriasis without PsA and a general population cohort.

METHODS

A cohort study was conducted using data from the Clinical Practice Research Datalink (CPRD), which is generally representative of the UK population[12] and contains anonymised primary care medical records for ~15 million individuals.

The study period was from 1 January 1998 to 31 December 2014. A cohort of patients with incident PsA were identified in the CPRD who were 18–89 years at diagnosis and had ≥1 year of up-to-standard (UTS) data contribution prior to the diagnosis date. Cases of PsA were matched at a 1:4 ratio to two randomly selected cohorts based on date of PsA diagnosis (their index date), year of birth, sex and general practice: the first matched cohort (general population cohort) included patients with no psoriasis, no PsA and no other inflammatory arthritis diagnoses, and the second cohort (psoriasis cohort) included patients with psoriasis but no diagnosis of PsA or other inflammatory arthritis. Patients in the comparator cohorts were assigned the index date of the matched case and were required to have ≥1 year of UTS data prior to their index date. All patients were followed from the index date until the date they were no longer eligible for the cohort or were diagnosed

Table 1 Baseline characteristics of the PsA, psoriasis and general population cohorts

	PsA		Psoriasis cohort		General population cohort	
	N	%	N	%	N	%
N	6783		27132		27132	
Sex (% male)	3327	49.05	13308	49.05	13308	49.05
Median age*, years (IQR)	49	(39–59)	49	(39–59)	49	(39–59)
Mean follow-up postindex, years (SD)	5.8	(4.1)	5.5	(4.1)	5.5	(4.1)
Mean duration of psoriasis,* years (SD)	11.3	(10.9)	11.8	(10.6)	–	–
Uveitis prevalence†‡	100	1.47	205	0.76	193	0.71
Inflammatory bowel disease prevalence†	51	0.75	323	1.19	249	0.92
Crohn's disease†	16	0.24	122	0.45	95	0.35
Ulcerative colitis†	24	0.35	150	0.55	127	0.47

*On index date.
†≥1 diagnosis recorded in the CPRD on or before the index date.
‡Of all the uveitis records identified, 71.5% were anterior, 1.5% were posterior, 0.3% were panuveitis, and for 26.7% the anatomic subtype was unknown. There was one case of posterior uveitis in the PsA cohort and six cases in both the psoriasis and general population cohorts.
CPRD, Clinical Practice Research Datalink; PsA, psoriatic arthritis.

with the outcome of interest. Patients in the general population and psoriasis cohorts who developed psoriasis or PsA respectively after the index date had their person-time contribution censored the day before the diagnosis date.

The outcomes of interest were uveitis and IBD. Diagnoses were identified based on Read codes and IBD was categorised as 'Crohn's disease', 'ulcerative colitis' and 'other/unspecified'. A full description of the methods can be found in the online supplementary file 1.

Statistical analyses

The incidence of uveitis, all IBD, Crohn's disease and ulcerative colitis was calculated for each of the study cohorts. For each outcome, crude and adjusted relative risks (RR) were calculated using conditional Poisson regression to compare the risk in the PsA cohort with the psoriasis and general population cohorts. The adjusted models accounted for smoking status, body mass index and psoriasis severity on the index date. Analyses were performed using R V.3.3.0 (R Core Team, 2017).

RESULTS

We identified 6783 eligible incident cases of PsA that were matched to 27132 patients with psoriasis and 27132 patients from the general population. The median age at PsA diagnosis was 49 years (IQR 39–59). The baseline patient characteristics for each cohort are shown in table 1. The mean duration of follow-up postindex date was similar in all three cohorts at approximately 5.5 years. The baseline prevalence of uveitis was 2.07 times higher in the PsA cohort than the general population (95% CI 1.63 to 2.64).

The median age at incident uveitis and ulcerative colitis was lower in the PsA cohort than psoriasis and general population cohorts (table 2). The incidence and risk of uveitis were significantly higher in the PsA cohort than in the general population

Table 2 Incidence of uveitis and IBD in the PsA, psoriasis and general population cohorts

	Cases	Median age at diagnosis (IQR)	Person-years	Incidence rate per 10000 person-years (95% CI)	
Uveitis					
General population	46*	55.0 (41.0–62.0)	146738	3.13	(2.30 to 4.18)
Psoriasis	74†	55.0 (48.0–65.0)	145482	5.09	(3.99 to 6.39)
PsA	42‡	47.0 (40.0–58.0)	38678	10.86	(7.83 to 14.68)
Inflammatory bowel disease (all)					
General population	67	55.0 (43.5–67.5)	146345	4.58	(3.55 to 5.81)
Psoriasis	67	53.0 (44.0–68.0)	144793	4.63	(3.59 to 5.88)
PsA	30	51.5 (42.0–60.0)	39077	7.68	(5.18 to 10.96)
Crohn's disease					
General population	25	50.0 (43.0–68.0)	146345	1.71	(1.11 to 2.52)
Psoriasis	22	50.5 (44.0–62.0)	144793	1.52	(0.95 to 2.30)
PsA	16	49.5 (33.0–56.5)	39077	4.09	(2.34 to 6.65)
Ulcerative colitis					
General population	35	57.0 (44.0–66.0)	146345	2.39	(1.67 to 3.33)
Psoriasis	38	60.5 (46.0–71.0)	144793	2.62	(1.86 to 3.60)
PsA	11	54.0 (46.0–61.0)	39077	2.81	(1.41 to 5.04)

*31 anterior, 15 subtype unknown.
†50 anterior, 1 panuveitis, 23 subtype unknown.
‡29 anterior, 1 panuveitis, 12 subtype unknown.
IBD, inflammatory bowel disease; PsA, psoriatic arthritis.

Table 3 Risk of uveitis and inflammatory bowel disease in patients with PsA compared with patients in the general population and patients with psoriasis

	PsA compared with a *general population cohort* (no PsA and no psoriasis)						PsA compared with a *psoriasis cohort* (psoriasis and no PsA)					
	Unadjusted			Adjusted*			Unadjusted			Adjusted†		
Comorbidity	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
Uveitis	3.83	2.45 to 5.99	<0.0001	3.55	2.21 to 5.70	<0.0001	2.17	1.46 to 3.22	<0.0001	2.13	1.40 to 3.24	<0.001
All inflammatory bowel disease	1.95	1.28 to 2.98	<0.0001	1.90	1.21 to 3.00	0.0056	1.71	1.13 to 2.61	<0.01	1.71	1.12 to 2.61	<0.05
Crohn's disease	3.08	1.64 to 5.80	<0.0001	2.96	1.46 to 6.00	0.0025	3.55	1.83 to 6.88	<0.0001	3.60	1.83 to 7.10	<0.001
Ulcerative colitis	1.30	0.68 to 2.46	0.43	1.30	0.66 to 2.56	0.44	1.08	0.58 to 2.02	0.80	0.98	0.50 to 1.92	0.96

*Adjusted for smoking status and body mass index (in the 3 months prior to the index date).
†Adjusted for smoking status and body mass index (in the 3 months prior to the index date) and psoriasis disease severity on the index date.
PsA, psoriatic arthritis; RR, relative risk.

and psoriasis cohorts (RR_{adj} 3.55, 95% CI 2.21 to 5.70 and RR_{adj} 2.13, 95% CI 1.40 to 3.24) (table 3). The incidence of all IBD was higher among patients with PsA, and when looking at Crohn's disease and ulcerative colitis separately, a significant increase was observed for Crohn's disease (RR_{adj} 2.96, 95% CI 1.46 to 6.00 and RR_{adj} 3.60, 95% CI 1.83 to 7.10 for general population and psoriasis cohorts, respectively) but not for ulcerative colitis (RR_{adj} 1.30, 95% CI 0.66 to 2.56 and RR_{adj} 0.98, 95% CI 0.50 to 1.92). Of interest, current smokers had a higher incidence of Crohn's disease than ex-smokers or non-smokers but the numbers were too small to be meaningful (data not shown).

DISCUSSION

This UK population-based study identified over a threefold and twofold increase in the risk of uveitis in patients with PsA when compared with the general population and patients with psoriasis respectively. A significant increase in risk was also observed for Crohn's disease among patients with PsA but this was not found for ulcerative colitis.

The increase in risk of uveitis associated with PsA, observed in our study, is in line with Danish and Taiwanese nationwide cohort studies.[5 6] The incidence rates of uveitis in our study, however, were approximately 50% higher than in the Danish cohorts and lower than the Taiwanese cohorts which may be related to differences in methods of data collection. Genetic factors may also play a role, given the close association between HLA-B27 and acute anterior uveitis,[13] although the background prevalence of HLA-B27 is lower in Taiwan than in the UK.[14] Nonetheless, a threefold increase in risk of uveitis compared with the general population is clinically meaningful in terms of prospectively managing and informing patients of potential relevant comorbidities. Furthermore, the risk appears more associated with PsA than with psoriasis, with the latter showing a similar baseline prevalence and incidence of uveitis to the general population. The baseline prevalence in the PsA cohort in our study is in line with an Irish study which included patients with ≤1 year PsA disease duration and reported a prevalence of uveitis of 1.55%[15] but is considerably lower than the 9.09% reported in an Italian study which also included newly diagnosed patients with <1 year disease duration.[16]

The increased risk observed between PsA and Crohn's disease, but not ulcerative colitis, is in line with a study by Li *et al*, using data from the Nurses' Health study in the USA.[11] The majority of other studies to date, however, have identified an increased risk for both Crohn's disease and ulcerative colitis, although many do report a higher magnitude of risk for Crohn's disease than ulcerative colitis.[7 9]

There are genes in risk loci common to psoriasis, PsA and Crohn's disease such as *IL12B*, *5q31*, *IL23R* and *IL2/IL21* that may explain our findings.[17] Dysbiosis leading to an upregulated Th17-driven immune response in a genetically susceptible host is another potential common pathogenic pathway.[18] Indeed, a recent study reported a specific dysbiosis in patients with spondylitis and a history of IBD.[19] Lifestyle factors such as smoking may also have an important role, especially considering that smoking is a known risk factor for Crohn's disease while smoking is associated with a lower risk of developing ulcerative colitis.[20] It is likely that an interaction of all these factors is important and worthy of study in larger data sets.

Strengths of our study include its population-based nature, the large number of patients with PsA, previous validation of the codes used to identify psoriasis and PsA, inclusion of both a psoriasis and general population-matched comparator group, and the length of follow-up after PsA diagnosis. The inclusion of only patients with incident PsA was an advantage for looking at the temporal relationship; however, one challenge when studying PsA, particularly when looking at comorbidities and risk factors, is disentangling preclinical PsA from psoriasis and/or delayed diagnosis.[21] It is therefore possible that some patients within the psoriasis only group may have actually had PsA and this could potentially have elevated the incidence rates in this group. In addition, as PsA is likely to develop some time before a patient visits their general practitioner, it is also possible that some patients identified as having prevalent disease, prior to their PsA diagnosis, may have developed the comorbidity of interest after the initial onset of PsA, but before a formal diagnosis was made, which would result in an underestimate of the incidence rates. Although unlikely for uveitis, assessment/detection bias could also have played a role for mild IBD cases, with patients with PsA being likely to visit their healthcare professionals more regularly than those in the comparator groups. Unfortunately, the absence of data on tumour necrosis factor-alpha inhibitor therapy in the CPRD meant it was not possible to explore the effect of PsA therapy on the incidence of uveitis and IBD.

The results of our study demonstrate an increased risk of developing uveitis and Crohn's disease in patients with PsA that in addition to pointing to shared genetic and pathogenic mechanisms has important implications for surveillance and management. More precise information on the estimated risk of these particular comorbidities can be shared with patients, alongside advice on lifestyle factors such as smoking, the latter of which in addition to its association with Crohn's disease[20] has also been shown to have a negative effect on long-term PsA outcome.[22]

Acknowledgements We wish to acknowledge the non-contributing authors of the PROMPT (early detection to imPRove OutcoMe in people with undiagnosed Psoriatic arthriTis) study group who have been responsible for the acquisition of funding and general supervision of the research group.

Collaborators PROMPT study group includes: Sarah Hewlett, Helen Harris, Philip Helliwell, Laura Coates, Catherine Fernandez, Sarah Brown, Claire Davies, Jonathan Packham, Laura Bjoke, Eldon Spakman, Anne Barton, Oliver Fitzgerald, Vishnu Madhok, Melanie Brooke, Jana James and Andrew Parkinson.

Contributors WT, NM, AN, GS and CHS contributed to the conception of the study. All authors contributed to the design of the work. Data acquisition and analysis was carried out by RC, JS, AN, AG and GS. All authors were involved in the interpretation of the study results as well as the drafting and revision of the manuscript and all approved the final version to be published.

Funding This report is an independent research funded by the National Institute for Health Research (Programme Grants for Applied Research, Early detection to improve outcome in patients with undiagnosed psoriatic arthritis, RP-PG-1212-20007). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Competing interests All authors report grants from the National Institute for Health Research (RP-PG-1212-20007) during the conduct of the study. CHS reports grants from the Medical Research Council (MR/L011808/1) outside the submitted work. AN and GS report grants from Pfizer and Celgene outside the submitted work.

Ethics approval Ethical approval has been obtained by the CPRD data provider from a Multi-centre Research Ethics Committee (MREC) for all observational studies and the study protocol was approved by the CPRD Independent Scientific Advisory Committee (15_154R).

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Ogdie A, Weiss P. The epidemiology of psoriatic arthritis. *Rheum Dis Clin North Am* 2015;41:545–68.
2 Rosen CF, Mussani F, Chandran V, *et al*. Patients with psoriatic arthritis have worse quality of life than those with psoriasis alone. *Rheumatology* 2012;51:571–6.
3 Tillett W, de-Vries C, McHugh NJ. Work disability in psoriatic arthritis: a systematic review. *Rheumatology* 2012;51:275–83.
4 Ogdie A, Schwartzman S, Husni ME. Recognizing and managing comorbidities in psoriatic arthritis. *Curr Opin Rheumatol* 2015;27:118–26.
5 Egeberg A, Khalid U, Gislason GH, *et al*. Association of psoriatic disease with uveitis: a danish nationwide cohort study. *JAMA Dermatol* 2015;151:1200–5.
6 Chi CC, Tung TH, Wang J, *et al*. Risk of uveitis among people with psoriasis: a nationwide cohort study. *JAMA Ophthalmol* 2017;135.
7 Egeberg A, Mallbris L, Warren RB, *et al*. Association between psoriasis and inflammatory bowel disease: a Danish nationwide cohort study. *Br J Dermatol* 2016;175:487–92.
8 Makredes M, Robinson D, Bala M, *et al*. The burden of autoimmune disease: a comparison of prevalence ratios in patients with psoriatic arthritis and psoriasis. *J Am Acad Dermatol* 2009;61:405–10.
9 Wu JJ, Nguyen TU, Poon KY, *et al*. The association of psoriasis with autoimmune diseases. *J Am Acad Dermatol* 2012;67:924–30.
10 Zohar A, Cohen AD, Bitterman H, *et al*. Gastrointestinal comorbidities in patients with psoriatic arthritis. *Clin Rheumatol* 2016;35:2679–84.
11 Li WQ, Han JL, Chan AT, *et al*. Psoriasis, psoriatic arthritis and increased risk of incident Crohn's disease in US women. *Ann Rheum Dis* 2013;72.
12 Herrett E, Gallagher AM, Bhaskaran K, *et al*. Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;44:827–36.
13 Brewerton DA, Caffrey M, Nicholls A, *et al*. Acute anterior uveitis and HL-A 27. *Lancet* 1973;302:994–6.
14 Hou TY, Chen HC, Chen CH, *et al*. Usefulness of human leucocyte antigen-B27 subtypes in predicting ankylosing spondylitis: Taiwan experience. *Intern Med J* 2007;37:749–52.
15 Kane D, Stafford L, Bresnihan B, *et al*. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. *Rheumatology* 2003;42:1460–8.
16 Niccoli L, Nannini C, Cassarà E, *et al*. Frequency of iridocyclitis in patients with early psoriatic arthritis: a prospective, follow up study. *Int J Rheum Dis* 2012;15:414–8.
17 Roberson ED, Bowcock AM. Psoriasis genetics: breaking the barrier. *Trends Genet* 2010;26:415–23.
18 Eppinga H, Konstantinov SR, Peppelenbosch MP, *et al*. The microbiome and psoriatic arthritis. *Curr Rheumatol Rep* 2014;16:407.
19 Breban M, Tap J, Leboime A, *et al*. Faecal microbiota study reveals specific dysbiosis in spondyloarthritis. *Ann Rheum Dis* 2017;76:1614–22.
20 Calkins BM. A meta-analysis of the role of smoking in inflammatory bowel disease. *Dig Dis Sci* 1989;34:1841–54.
21 Ogdie A. The preclinical phase of PsA: a challenge for the epidemiologist. *Ann Rheum Dis* 2017;76:1481–3.
22 Tillett W, Jadon D, Shaddick G, *et al*. Smoking and delay to diagnosis are associated with poorer functional outcome in psoriatic arthritis. *Ann Rheum Dis* 2013;72:1358–61.

EXTENDED REPORT

Predictors of revision, prosthetic joint infection and mortality following total hip or total knee arthroplasty in patients with rheumatoid arthritis: a nationwide cohort study using Danish healthcare registers

Rene Lindholm Cordtz,[1,2] Kristian Zobbe,[1,2] Pil Højgaard,[1,2] Lars Erik Kristensen,[2] Søren Overgaard,[3,4] Anders Odgaard,[5,6] Hanne Lindegaard,[4,7] Lene Dreyer[1,2,6]

Handling editor Josef S Smolen

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-212339).

For numbered affiliations see end of article.

Correspondence to
Dr Rene Lindholm Cordtz, Center for Rheumatology and Spine Diseases, Rigshospitalet - Gentofte, Kildegaardsvej 28, 2900-Hellerup, Denmark; rene.lindholm.cordtz.03@regionh.dk

Received 5 September 2017
Revised 19 October 2017
Accepted 22 October 2017
Published Online First 2 November 2017

ABSTRACT

Objectives To investigate predictors of 10-year risk of revision and 1-year risk of prosthetic joint infection (PJI) and death following total hip/total knee arthroplasty (THA/TKA) in (1) patients with rheumatoid arthritis (RA) compared with patients with osteoarthritis (OA); and (2) patients with RA treated with biological disease-modifying antirheumatic drugs (bDMARD) within 90 days preceding surgery compared with non-treated.

Methods Register-based cohort study using the Danish National Patient Register, the DANBIO rheumatology register (RA-specific confounders and treatment episodes) and the Danish Hip and Knee Arthroplasty Registers. Survival analyses were used to calculate confounder-adjusted sub-HRs (SHR) and HRs.

Results In total, 3913 patients with RA with THA/TKA were compared with 120 499 patients with OA. Patients with RA had decreased risk of revision (SHR 0.71 (0.57–0.89)), but increased risk of PJI (SHR=1.46 (1.13–1.88)) and death (HR=1.25 (1.01–1.55)). In DANBIO, 345 of 1946 patients with RA with THA/TKA had received bDMARD treatment within 90 days preceding surgery. bDMARD-treated patients did not have a statistically significant increased risk of revision (SHR=1.49 (0.65–3.40)), PJI (SHR=1.61 (0.70–3.69)) nor death (HR=0.75 (0.24–2.33)) compared with non-treated. Glucocorticoid exposure (HR=2.87 (1.12–7.34)) and increasing DAS28 (HR=1.49 (1.01–2.20)) were risk factors for mortality.

Conclusion Patients with RA had a decreased 10-year risk of revision while the risk of death and PJI was increased compared with patients with OA following THA/TKA. bDMARD exposure was not associated with statistically significant increased risk of neither PJI nor death in this study. Glucocorticoid exposure and increased disease activity were associated with an increased risk of death.

BACKGROUND

The introduction of biological disease-modifying antirheumatic drugs (bDMARD) has improved the treatment of patients with rheumatoid arthritis (RA), but due to their immunosuppressive actions, they could potentially increase the risk of prosthetic joint infection (PJI) following major joint surgery such as total hip arthroplasty (THA) and total knee arthroplasty (TKA).[1 2] PJI is a serious complication associated with inferior outcomes in terms of pain, morbidity and mortality[3]; and it constitutes an economic burden in healthcare budgets with longer duration of hospital stays, extensive antibiotic treatment and prolonged recovery.[4] Most,[5–11] but not all studies,[7 8] have found increased risk of PJI and surgical complications in patients with RA following THA and TKA but not with regard to the overall risk of revision.[12] Results have been contradictory as to whether bDMARD treatment affects the risk of PJI.[2 13–15]

Patients with RA have increased mortality rates compared with the general population. However, with few exceptions,[16 17] existing studies have reported no difference or decreased risk of short-term mortality in RA compared with other THA/TKA recipients.[5–10] It is unknown whether bDMARD treatment affects the mortality risk.

The aim of this study was to estimate the risk of revision due to non-infectious causes, PJI and death among patients with RA following primary THA or TKA. We compared (1) patients with RA with patients with osteoarthritis (OA) and (2) bDMARD-treated with non-bDMARD-treated patients with RA using Danish healthcare registers. Further, we aimed at estimating the impact of glucocorticoid treatment and disease activity on the risk of revision, PJI and death among patients with RA.

PATIENTS AND METHODS

Study design and setting

Register-based cohort study from Denmark from 1 January 2000 to 31 December 2014. Every Danish resident receives a 10-digit personal identification number consistent throughout all national registers making register linkage possible. Study methods and results are presented in accordance with Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[18]

Data sources

The Civil Registration System (CRS): registers dates of deaths and migrations among all Danish citizens.[19]

To cite: Cordtz RL, Zobbe K, Højgaard P, *et al*. *Ann Rheum Dis* 2018;**77**:281–288.

Table 1 Baseline characteristics of patients with RA and patients with OA who had primary total hip or knee arthroplasty during 2000–2014

		RA	OA	P value
Total, n		3913	120 499	
Age at surgery, mean (SD)		66.6 (11.3)	69.1 (9.8)	<0.001
Female sex, n (% of group)		2849 (72.8)	70 177 (58.2)	<0.001
Follow-up in years, mean (SD)		5.47 (3.3)	5.38 (3.3)	0.088
Primary THA/ TKA, n (% of cohort)		1677 (43)/2236 (57)	71 481 (59)/49 018 (41)	
THA	Cement with antibiotics	869 (52)	30 926 (43)	<0.001
	Cement without antibiotics	17 (1)	1286 (2)	
	Uncemented	766 (46)	38 321 (54)	
	Missing information	25 (2)	948 (1)	
TKA	Cement with antibiotics	1713 (77)	36 566 (75)	0.049
	Cement without antibiotics	18 (1)	409 (1)	
	Uncemented	454 (20)	11 113 (23)	
	Missing information	51 (2)	946 (2)	
Duration of surgery (min), mean (SD)		72.37 (23.0)	69.13 (23.3)	<0.001
Calendar period of surgery, n (%)	2000–2002	748 (19)	17 788 (15)	<0.001
	2003–2005	741 (19)	20 260 (17)	
	2006–2008	757 (19)	25 488 (21)	
	2009–2011	852 (22)	29 446 (24)	
	2012–2014	815 (21)	27 517 (23)	
Previously hospitalised due to infection, n (%)		1041 (27)	15 439 (13)	<0.001
Chronic obstructive pulmonary disease, n (%)		332 (9)	5283 (4)	<0.001
Diabetes mellitus, n (%)		323 (8)	7016 (6)	<0.001
Diagnosed with obesity, n (%)		290 (7)	8307 (7)	0.219
Ischaemic heart disease, n (%)		204 (5)	4582 (4)	<0.001

OA, osteoarthritis; RA, rheumatoid arthritis; THA, total hip arthroplasty; TKA, total knee arthroplasty.

The National Patient Register (NPR): includes information on all inpatient (1977–) and outpatient (1995–) visits at Danish hospitals.[20] Discharge diagnoses are registered in accordance with the International Classification of Diseases (ICD) (ICD-8: 1977–1993; ICD-10: 1994–) with up to 20 diagnoses for each discharge.

DANBIO: established in 2000 as a national register for use and efficacy of bDMARDs in treatment of inflammatory arthritis (coverage >91%), and more than 25 000 patients with RA are registered. [21] Information includes date of diagnosis, anti-rheumatic treatment series, Health Assessment Questionnaire Disability Index (HAQ-DI), Disease Activity Score using the 28-joint count (DAS28) and C-reactive protein (CRP).

Danish Hip Arthroplasty Register (DHR): is a nationwide register used for mandatory registration of all primary and revision THA surgeries established in 1995.[22] The coverage for primary THA surgery is 97%. Only PJIs treated with surgery are registered in DHR.[23]

Danish Knee Arthroplasty Register (DKR): established in 1997, DKR is a nationwide database in which orthopaedic surgeons register all primary and revision TKA surgeries.[24] In 2010, the completeness of registration was estimated to 97% for both primary and revision surgeries.

Study population

Patients with RA. Patients with RA were identified in DANBIO and NPR. Until 2006, only patients treated with bDMARDs were mandatorily registered in DANBIO. To include more bDMARD-naive patients, we identified patients registered in NPR with a diagnosis of RA at an inpatient or outpatient facility specialised in rheumatology or general internal medicine.[25] Identified patients with RA were subsequently linked with DHR and DKR to identify those with primary THA/TKA during 2000–2014. Only surgeries performed after RA diagnosis were included; and patients only contributed with their first primary THA/TKA in case of multiple (eg, bilateral THA/TKA). Patients were excluded if, according to DHR/DKR, THA/TKA was performed

Table 2 Number of patients with RA and patients with OA and associated PY of observation, events and crude rate ratios (95% CI) for 10-year risk of revision due to non-infectious reasons, and 1-year risk of prosthetic joint infection and death, respectively

Outcome		RA	OA
10-year risk of revision	Number of patients	3913	120 499
	Person-years of observation	20 900	642 739
	Number of revisions	81	3031
	Crude incidence rate per 1000 PY	3.9 (3.1–4.8)	4.7 (4.6–4.9)
	Rate ratio (95% CI)	0.82 (0.66 to 1.03)	Ref
1-year risk of prosthetic joint infection	Person-years of observation	3652	112 660
	Number of PJIs	63	1226
	Registered as revision in DHR/DKR	40	1037
	Crude incidence rate per 1000 PY	17.3 (13.5–22.1)	10.9 (10.3–11.5)
	Rate ratio (95% CI)	1.59 (1.23 to 2.05)	Ref
1-year risk of death	Person-years of observation	3746	115 007
	Number of deaths	86	2077
	Crude mortality rate per 1000 PY	23.0 (18.6–28.4)	18.1 (17.3–18.9)
	Rate ratio (95% CI)	1.27 (1.02 to 1.58)	Ref

DHR, Danish Hip Arthroplasty Register; DKR, Danish Knee Arthroplasty Register; OA, osteoarthritis; PJI, prosthetic joint infection; PY, person-years; RA, rheumatoid arthritis; Ref, reference.

Table 3 Long-term risk of revision due to other causes than PJI and 1-year risks of PJI and death among patients with RA compared with patients with OA following total hip or knee arthroplasty

		10-year risk of revision			1-year risk of prosthetic joint infection			1-year risk of death		
		Univariate	Model 1	Model 2	Univariate	Model 1	Model 2	Univariate	Model 1	Model 2
		SHR (95% CI)	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
RA versus OA		0.79 (0.64 to 0.99)	0.76 (0.61 to 0.95)	0.71 (0.57 to 0.89)	1.59 (1.23 to 2.04)	1.70 (1.32 to 2.19)	1.46 (1.13 to 1.88)	1.27 (1.02to 1.58)	1.58 (1.27 to 1.96)	1.25 (1.01 to 1.55)
Female versus male		0.91 (0.85 to 0.98)	0.96 (0.89 to 1.03)	0.95 (0.89 to 1.02)	0.72 (0.65 to 0.80)	0.70 (0.63 to 0.78)	0.70 (0.63 to 0.78)	0.63 (0.58 to 0.69)	0.53 (0.49 to 0.58)	0.56 (0.51 to 0.61)
Age at surgery (years)		0.98 (0.98 to 0.98)	0.98 (0.98 to 0.98)	0.98 (0.98 to 0.98)	1.01 (1.00 to 1.01)	1.01 ((1.00 to 1.02)	1.01 (1.00 to 1.01)	1.09 (1.09 to 1.09)	1.08 (1.08 to 1.09)	1.08 (1.07 to 1.08)
Calendar year of surgery	2000–2002	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	2003–2005	0.93 (0.83 to 1.04)	0.93 (0.83 to 1.03)	0.91 (0.81 to 1.01)	1.11 (0.91 to 1.35)	1.14 (0.93 to 1.38)	1.10 (0.90 to 1.34)	0.88 (0.77 to 1.00)	0.90 (0.79 to 1.02)	0.85 (0.74 to 0.97)
	2006–2008	1.06 (0.95 to 1.17)	1.04 (0.94 to 1.16)	1.02 (0.91 to 1.13)	1.18 (0.99 to 1.42)	1.25 (1.04 to 1.51)	1.21 (1.00 to 1.45)	0.76 (0.67 to 0.86)	0.83 (0.73 to 0.95)	0.78 (0.69 to 0.89)
	2009–2011	1.14 (1.02 to 1.27)	1.12 (1.00 to 1.25)	1.08 (0.96 to 1.20)	1.03 (0.86 to 1.24)	1.11 (0.92 to 1.33)	1.05 (0.87 to 1.27)	0.66 (0.58 to 0.75)	0.75 (0.66 to 0.85)	0.68 (0.60 to 0.78)
	2012–2014	1.18 (1.03 to 1.35)	1.17 (1.02 to 1.33)	1.09 (0.96 to1.25)	1.08 (0.89 to 1.30)	1.17 (0.96 to 1.41)	1.07 (0.88 to 1.29)	0.50 (0.43 to 0.58)	0.56 (0.48 to 0.66)	0.49 (0.42 to 0.57)
Duration of surgery (hours)		0.87 (0.79 to 0.97)		0.91 (0.82 to 1.01)	1.25 (1.15 to 1.35)	1.25 (1.15 to 1.36)	1.23 (1.12 to 1.35)	1.38 (1.30 to 1.46)	1.29 (1.19 to 1.39)	1.25 (1.15 to 1.37)
Previously hospitalised due to infection		1.40 (1.27 to 1.54)		1.48 (1.34 to 1.64)	2.11 (1.86 to 2.40)		1.92 (1.67 to 2.22)	2.79 (2.54 to 3.06)		1.98 (1.79 to 2.18)
Ischaemic heart disease		1.15 (0.97 to 1.36)		1.18 (0.99 to 1.40)	1.53 (1.21 to 1.94)		1.17 (0.92 to 1.49)	2.84 (2.47 to 3.27)		1.62 (1.40 to 1.87)
COPD		1.23 (1.05 to 1.44)		1.17 (0.99 to 1.37)	1.88 (1.54 to 2.29)		1.41 (1.14- to 0.74)	3.21 (2.83 to 3.64)		2.01 (1.77 to 2.30)
Diabetes mellitus		1.01 (0.87 to 1.18)		0.95 (0.81 to 1.11)	1.66 (1.38 to 2.01)		1.35 (1.11 to 1.64)	2.40 (2.11 to 2.72)		1.90(1.67 to 2.16)

COPD, chronic obstructive pulmonary disease; OA, osteoarthritis; PJI, prosthetic joint infection; RA, rheumatoid arthritis; Ref, reference; SHR. sub-HR.

for reasons other than RA or OA sequelae (eg, fracture, avascular necrosis etc.).

Patients with OA. In DHR and DKR, we identified patients with a first primary THA/TKA due to OA and no history of RA.

bDMARD treatment in patients with RA. Patients with RA registered in DANBIO were used for these analyses to obtain information on treatment episodes of DMARD and glucocorticoids as well as disease activity and severity markers. For each patient, information on start and stop dates for treatment episodes was obtained and categorised according to drug types (bDMARD, conventional synthetic DMARD (csDMARD) and glucocorticoid).[21] bDMARD, csDMARD or glucocorticoid exposure was defined as treatment within 90 days preceding surgery. bDMARD-treated patients were compared with patients registered in DANBIO who had not been exposed to bDMARDs during this 90-day window (non-bDMARD treated).

Outcomes

Primary outcomes were 10-year risk of revision for non-infectious reasons, 1-year risk of PJI treated with or without surgery[23] and 1-year risk of death following primary THA/TKA. Revision and PJIs treated surgically were captured in DHR and DKR where the cause of revision surgery is preoperatively registered by the surgeon. The positive predictive value (PPV) of PJI in DHR is 66%.[26] We further captured PJIs not registered in DHR/DKR using the NPR (ICD-10: T84.5, infection and inflammatory reaction due to internal joint prosthesis; PPV=85%).[27] Mortality data were obtained by linkage to CRS. Secondary outcomes were 10-year risk of PJI and death.

Follow-up

Follow-up started at date of primary THA/TKA. In analyses of revision, follow-up ended at date of revision, PJI, death, emigration, at 10 years of follow-up or the end of 2014, whichever came first. In PJI analyses, follow-up ended at date of PJI, death, emigration, end of 2014 or at 1 year of follow-up, whichever came first. In mortality analyses, follow-up ended at date of death, emigration, end of 2014 or at 1 year of follow-up, whichever came first.

Confounders

Demographics

All multivariable analyses were adjusted for age at surgery, sex, calendar period and duration of surgery.

Comorbidities

Through linkage with NPR, we obtained information on diagnoses of chronic obstructive pulmonary disease (COPD), diabetes mellitus, ischaemic heart disease and hospitalisation due to infection with a look-back window of 20 years (see online supplementary table 1 for details).

RA-specific confounders

We adjusted for seropositive RA (DANBIO-reported positive IgM-rheumatoid factor and/or anti-citrullinated protein antibodies; or an ICD-10 code of seropositive RA (M05.8/M05.9) in NPR). For DANBIO patients, registration of DAS28-CRP and HAQ-DI within 1 year prior to surgery was obtained.

Statistical analyses

Demographic and descriptive data are presented as means and SDs. Groups were compared by independent t-test and χ^2 test as appropriate. For each exposure group and outcome, the number

Table 4 Baseline characteristics of patients with rheumatoid arthritis registered in DANBIO who received a bDMARD within 90 days prior to total hip or knee arthroplasty compared with non-bDMARD-treated patients

		bDMARD treated*	Non-bDMARD treated	P value
Total, n		345	1601	
Age at surgery, mean (SD)		61.3 (12.0)	65.2 (10.7)	<0.001
Female sex (% of group)		246 (71)	1182 (74)	0.480
Mean follow-up time		4.7 (3.4)	5.9 (3.4)	<0.001
Duration of surgery (min), mean (SD)		72 (23)	72 (23)	0.927
Calendar year of surgery, n (%)	2000–2004	61 (18)	465 (29)	<0.001
	2005–2009	136 (39)	511 (32)	
	2010–2014	148 (43)	625 (39)	
Seropositive (ACPA and/or IgM-RF), n (%)		310 (90)	1357 (85)	0.014
DAS28-CRP, mean (SD)		5.02 (1.43)	3.82 (1.48)	<0.001
Categorised DAS28-CRP†	Remission	66 (26)	93 (28)	<0.001
	Low	51 (20)	79 (24)	
	Moderate	111 (44)	131 (39)	
	High	25 (10)	30 (9)	
HAQ-DI, mean (SD)†		1.34 (0.74)	1.12 (0.76)	<0.001
Treated with TNFi (%)		321 (93)		
Treated with csDMARD (%)		216 (54)	519 (29)	<0.001
Treated with glucocorticoids (%)		200 (58)	493 (31)	<0.001
Previously hospitalised due to infection (%)		99 (29)	404 (25)	0.183
COPD, n (%)		24 (7)	114 (7)	0.895
Diabetes mellitus, n (%)		18 (5)	114 (7)	0.634
Diagnosed with obesity, n (%)		19 (6)	115 (7)	0.318
Ischaemic heart disease, n (%)		13 (4)	68 (4)	0.328

*Type of bDMARD: adalimumab 103; certolizumab 3; etanercept 124; infliximab 93; tocilizumab 25 (3 switched bDMARD during the 3 months preceding surgery, resulting in 348 treatment series among 345 patients: 1 switched from infliximab to adalimumab, 1 from adalimumab to tocilizumab and 1 from etanercept to adalimumab).
†Non-imputed values.
ACPA, anti-citrullinated protein antibody; bDMARD, biological DMARD; COPD, chronic obstructive pulmonary disease; csDMARD, conventional synthetic DMARD; DAS28-CRP, Disease Activity Score using the 28-joint count and C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; IgM-RF, immunoglobulin M rheumatoid factor; TNFi, tumour necrosis factor-alpha inhibitor.

of events, person-years at risk, crude incidence rates and rate ratios with 95% CIs were calculated.

Univariable and multivariable Fine-Gray competing risks regression analyses were used to calculate sub-HRs (SHR) for revision and PJI, whereas Cox proportional hazard models were used to calculate HRs for death. Time since surgery was used as underlying time scale in all models. The proportional hazard assumption was checked by tests based on Schoenfeld residuals. Different confounder adjustment approaches were applied in multivariable analyses as described below.

Analyses of patients with RA versus patients with OA

(1) A basic model containing age at surgery (1-year increments), sex, calendar time of surgery (2000–2002, 2003–2005, 2006–2008, 2009–2011, 2012–2014) and duration of surgery. (2) A model that further included adjustment for comorbidities.

Analyses of bDMARD-treated compared with non-bDMARD-treated patients with RA

First, a basic model with bDMARD treatment (yes/no) as the key exposure variable and adjusted for age at surgery, sex and calendar period of surgery (2000–2009 vs 2010–2014) was created. Due to few events and our main interest being impact of bDMARD treatment, we used the change-of-estimate approach to decide on confounders to be included in the final model.[28] Covariates changing the SHR/HR with ≥10% for the bDMARD exposure variable when added to the basic model were tested in a stepwise forward-selection manner. Tested covariates are listed in the confounder section above. We tested for (and found no) effect modification between bDMARD and glucocorticoid exposure, and csDMARD and glucocorticoid exposure on each of the outcomes.

Multiple imputation

Due to missing values for DAS28-CRP and HAQ, multiple imputation by chained equations (MICE) was carried out using the MI suite in Stata[29] (see online supplementary files).

In all tests, P values <0.05 were considered statistically significant. Statistical analyses were performed using Stata (V.13.1, StataCorp, Texas, USA) and R V.3.3.0.[30]

Sensitivity analyses

Sensitivity analyses included adjustment for comorbidities using the Charlson Comorbidity Index (CCI) (see online supplementary table 2).[31] Also, to distinguish a potential spike in mortality caused by surgery from the generally increased mortality associated with RA, we calculated crude mortality rates, and adjusted HRs for years 0–1 and 1–10 after surgery.

In exploratory analyses, we investigated if there was a dose–response effect of glucocorticoid exposure on risks of PJI and death comparing users treated with doses ≤7.5 mg and doses >7.5 mg, respectively with non-users.[32] Similarly, we compared patients who received intra-articular/ intramuscular glucocorticoid injections prior to surgery with glucocorticoid non-users.

Table 5 Number of patients with rheumatoid arthritis treated and not treated with bDMARDs within 90 days prior to surgery, respectively, and associated person-years of observation, events and crude rate ratios (95% CI) for 10-year risk of revision due to other causes than PJI and 1-year risks of PJI and death

Outcome		bDMARD treated	Non-bDMARD treated
10-year risk of revision	Number of patients	345	1601
	Person-years of observation	1712	9027
	Number of revisions	9	28
	Crude incidence rate per 1000 PY	5.3 (2.7–10.1)	3.1 (2.1–4.5)
	Rate ratio (95% CI)	1.63 (0.78 to 3.42)	Ref
1-year risk of prosthetic joint infection	Person-years of observation	318	1497
	Number of PJIs	9	28
	Registered as revision in DHR/DKR	7	19
	Crude incidence rate per 1000 PY	28.3 (14.7–53.3)	18.7 (12.9–27.1)
	Rate ratio (95% CI)	1.50 (0.71 to 3.19)	Ref
1-year risk of death	Person-years of observation	329	1535
	Number of deaths	5	19
	Crude mortality rate per 1000 PY	15.2 (6.3–36.6)	12.4 (7.9–19.4)
	Rate ratio (95% CI)	1.24 (0.46 to 3.33)	Ref

bDMARD, biological DMARD; DHR, Danish Hip Arthroplasty Register; DKR, Danish Knee Arthroplasty Register; PJI, prosthetic joint infection; PY, person-years; Ref, reference.

RESULTS

Patients with RA compared with patients with OA

Following register linkage, 3913 patients with RA and primary THA/TKA were available for comparison with 120 499 patients with OA (patient flow chart in online supplementary figure 1). Patients with RA were more likely to be female, younger at time of surgery and suffer from comorbidities (table 1).

Revision

Of 3913 patients with RA, 81 had surgical revision for reasons other than PJI within 10 years of primary THA/TKA resulting in a crude rate ratio of 0.82 (95% CI 0.66 to 1.03) for revision (table 2). A decreased risk of revision among patients with RA remained in the final multivariable model (table 3).

Prosthetic joint infection

Within a year of surgery, 63 patients with RA had a PJI, and were at increased risk of PJI in univariable and multivariable analyses with a final adjusted SHR of 1.46 (95% CI 1.13 to 1.88) (tables 2 and 3). Other risk factors for PJI were male sex, increasing duration of surgery, a history of hospitalisation due to infection, COPD and diabetes mellitus (table 3).

Death

During the first year, 86 patients with RA died and RA was associated with increased mortality risk in univariable and multivariable analyses (HR in final adjusted model 1.25; 95% CI 1.01 to 1.55) (table 2). Other risk factors were comorbidities and increasing duration of surgery, whereas women had a decreased risk of death.

bDMARD-treated compared with non-bDMARD-treated patients with RA

In DANBIO, 1946 patients with RA and primary THA/TKA were identified. Of these, 345 had received bDMARD treatment within 90 days preceding surgery (table 4). On average, bDMARD-treated patients were younger at time of surgery, had higher DAS28-CRP and HAQ-DI, and a higher proportion was seropositive and treated with concomitant csDMARD and glucocorticoids (table 4).

Revision

Nine revisions occurred among the 345 bDMARD-treated compared with 28 among 1601 non-bDMARD-treated patients (table 5). In the basic model, the SHR for long-term revision was 1.69 (95% CI 0.79 to 3.61) among bDMARD-treated compared with non-bDMARD-treated patients (table 6). Following the change-of-estimate procedure, glucocorticoid was added to the final model resulting in an SHR of 1.49 (95% CI 0.65 to 3.40).

Prosthetic joint infection

Only nine PJI cases were observed in the first year following surgery among bDMARD-treated patients (table 5). Following the change-in-estimate procedure, glucocorticoid exposure and DAS28-CRP were added to the model resulting in an SHR of 1.61 (0.70–3.69) for PJI among bDMARD-treated patients (table 6).

Death

Five deaths occurred among 329 bDMARD-treated patients during the first year following surgery resulting in an HR of 1.44 (95% CI 0.53 to 3.88) in the basic model compared with non-bDMARD-treated patients (tables 5 and 6). This estimate, however, was reduced to 0.75 (95% CI 0.24 to 2.33) when glucocorticoid treatment was added to the model (table 6).

Sensitivity analyses

Adjusting for CCI did not change the results in analyses of RA compared with OA nor bDMARD-treated compared with non-bDMARD-treated patients (online supplementary tables 3 and 4). Analysing 10-year risk of PJI and death in patients with RA compared with OA increased the risk estimates (PJI: SHR=1.84 (1.55–2.18); death: HR=1.58 (1.47–1.69)) (online supplementary table 5). Mortality rates among patients with RA in years 0–1 compared with years 1–10 did not reveal increased mortality in the first year compared with later years (HR 1.26 (1.01–1.56) in year 0–1 vs 1.62 (1.51–1.75) in years 1–10) (online supplementary table 6). Ten-year risk of PJI and death did not differ from 1-year risk among bDMARD-treated compared with non-bDMARD-treated patients (online supplementary table 7). For glucocorticoids, there was a dose–response relation on the risk of PJI and death with highest risk estimates observed among users treated with doses >7.5 mg (PJI: SHR=3.21, 95% CI 1.07 to 9.67; death: HR=4.16, 95% CI 1.32 to 13.08), but users treated with doses ≤7.5 mg also had increased risk compared with non-users (PJI: SHR=1.21, 95% CI 0.35 to 4.15; death: HR=3.32, 95% CI 1.06 to 10.41) (online supplementary table 8). Intra-articular/intramuscular glucocorticoid injections within 90 days prior to surgery were associated with increased risk of death (HR=10.80, 95% CI 2.93 to 39.80) (online supplementary table 9).

Table 6 Ten-year risk of revision due to other causes than infection and 1-year risks of PJI and death following total hip and knee arthroplasty among patients with rheumatoid arthritis from DANBIO treated with bDMARDs within 90 days prior to surgery compared with non-bDMARD-treated patients

		10-year risk of revision			1-year risk of prosthetic joint infection			1-year risk of death		
		Univariate, n=1946	Basic model, n=1946	Adjusted model, n=1936	Univariate, n=1946	Basic model, n=1946	Adjusted model, n=1936	Univariate, n=1946	Basic model, n=1946	Adjusted model, n=1858
		SHR (95% CI)	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
bDMARD versus non-bDMARD treated		1.59 (0.74 to 3.38)	1.69 (0.79 to 3.61)	1.49 (0.65 to 3.40)	1.51 (0.71 to 3.19)	1.53 (0.71 to 3.30)	1.61 (0.70 to 3.69)	1.24 (0.46 to 3.32)	1.44 (0.53 to 3.88)	0.75 (0.24 to 2.33)
Female versus male		1.55 (0.68 to 3.54)	1.56 (0.68 to 3.54)	1.57 (0.69 to 3.60)	1.89 (0.79 to 4.53)	1.92 (0.80 to 4.60)	1.73 (0.70 to 4.28)	1.09 (0.43 to 2.75)	0.97 (0.39 to 2.46)	1.46 (0.54 to 3.89)
Age at surgery (years)		1.02 (0.99 to 1.05)	1.02 (0.99 to 1.05)	1.02 (0.99 to 1.05)	0.99 (0.97 to 1.02)	1.00 (0.97 to 1.03)	1.00 (0.97to 1.03)	1.13 (1.07 to 1.18)	1.13 (1.08 to 1.19)	1.12 (1.07 to 1.18)
Calendar year of surgery	2000–2010	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	2011–2014	1.30 (0.54 to 3.14)	1.22 (0.50 to 3.01)	1.19 (0.47 to 2.99)	0.63 (0.29 to 1.38)	0.65 (0.29 to 1.45)	1.05 (0.43 to 2.58)	1.31 (0.56 to 3.06)	1.15 (0.49 to 2.77)	1.24 (0.49 to 3.10)
Duration of surgery (hours)		0.89 (0.35 to 2.23)	0.93 (0.37 to 2.33)	0.91 (0.36 to 2.30)	1.35 (0.56 to 3.23)	1.27 (0.49 to 3.29)	1.03 (0.33 to 3.28)	2.80 (1.35 to 5.82)	3.25 (1.58 to 6.69)	2.55 (1.22 to 5.33)
TNFi		1.69 (0.79 to 3.59)			1.19 (0.52 to 2.70)			1.03 (0.-35 to 3.00)		
csDMARD		1.11 (0.55 to 2.26)			1.25 (0.65 to 2.41)			2.26 (1.01 to 5.04)		
Methotrexate		1.12 (0.52 to 2.41)			1.56 (0.79 to 3.06)			1.77 (0.78 to 4.05)		
Glucocorticoid		1.87 (0.82 to 4.26)		1.68 (0.67 to 4.20)	2.31 (1.09 to 4.89)		2.12 (0.90 to 4.98)	3.68 (1.58 to 8.60)		2.87 (1.12-7.34)
Previously hospitalised with infection		1.34 (0.66 to 2.71)			1.99 (1.03 to 3.83)			3.47 (1.56 to 7.75)		
Ischaemic heart disease		No events			2.03 (0.62 to 6.63)			2.12 (0.50 to 9.03)		
COPD		3.14 (1.32 to 7.47)			2.13 (0.83 to 5.48)			1.23 (0.29 to 5.23)		
DM		0.80 (0.19 to 3.32)			1.67 (0.59 to 4.72)			No events among patients with DM		
Ischaemic heart disease, COPD or DM		1.40 (0.62 to 3.18)			1.30 (0.57 to 2.97)			1.12 (0.38 to 3.29)		
Serostatus	Seronegative	Ref			No events			No events		
	Seropositive (IgM-RF or ACPA)	2.77 (0.67 to 11.55)			38 events			24 events		
DAS28-CRP		0.70 (0.44 to 1.13)			1.98 (1.28 to 3.05)		2.00 (1.28 to 3.13)	1.49 (1.01 to 2.20)		
HAQ-DI		1.48 (0.64 to 3.43)			1.51 (0.68 to 3.36)			2.68 (1.30 to 5.53)		

ACPA, anti-citrullinated protein antibody; bDMARD, biological DMARD; COPD, chronic obstructive pulmonary disease; csDMARD, conventional synthetic DMARD; DAS28-CRP, Disease Activity Score using the 28-joint count and C-reactive protein; DM, diabetes mellitus; HAQ-DI, Health Assessment Questionnaire Disability Index; IgM-RF, immunoglobulin M rheumatoid factor; PJI, prosthetic joint infection; Ref, reference; SHR, sub-HR; TNFi, tumour necrosis factor-alpha inhibitor.

DISCUSSION

In this nationwide register-based cohort study, we investigated the risk of long-term revision due to non-infectious causes and 1-year risks of PJI and death among patients with RA following THA/TKA: our main findings were increased risks of PJI and death, but a decreased long-term risk of revision in patients with RA compared with patients with OA. bDMARD-treated patients with RA were not at increased risk of PJI nor death. Glucocorticoid treatment proved a significant risk factor for PJI and death with clear dose–response relations.

One previous study and a meta-analysis of two studies have also reported a decreased risk of revision among patients with RA.[8 12] Possible explanations for a reduced risk of revision are decreased wear of the implant due to lower physical activity in patients with RA compared with patients with OA, and surgeons possibly being less prone to perform revisions on patients with RA due to comorbidities and fragile bone stocks.[33 34] bDMARD treatment did not have an impact on the risk of revision, and we are not aware of other studies that have investigated this.

In line with previous studies, we found an increased risk of PJI among patients with RA.[7 10 11 35–37] In a study from Canada, Ravi *et al* reported an HR of 1.47 for the 2-year risk of PJI among patients with RA compared with patients with OA following TKA, similar to our 1-year risk estimate (HR 1.46).[7] We investigated the 1-year risk of PJI as most PJIs occur during this period.[23]However, in the analysis of 10-year risk of PJI, the risk estimates increased further (SHR 1.84). Scandinavian studies have reported increased risk of late, haematogenous PJIs among patients with RA compared with other THA/TKA recipients, which might explain the increase in long-term risk estimates in our study.[11 38 39] We did not find a statistically increased risk of PJI among patients with RA treated with bDMARDs. A meta-analysis from 2014 reported an increased risk of surgical site infection with perioperative exposure to tumour necrosis factor-alpha inhibitor treatment.[2] However, the meta-analysis was limited by the heterogeneity of the included studies and use of unadjusted estimates. Our results indicate that ongoing inflammation (high DAS28) and use of glucocorticoids may constitute even greater risk factors for PJI than bDMARD treatment. In accordance with our results, a recent study by George *et al* reported an increased risk of infection and PJI with perioperative glucocorticoid treatment (HR 2.70 for >10 mg/day compared with non-users) in relation to THA/TKA among 4288 patients receiving infliximab treatment for various inflammatory diseases.[15] We report even higher risk estimates with an SHR of 2.31 for PJI within the first year for glucocorticoid users (any dose); and a SHR of 4.88 for doses >7.5 mg compared with non-users. Crowson *et al* and Zink *et al* have published risk scores for serious infections in patients with RA that support our findings: glucocorticoid exposure increases the risk of serious infections in a dose-dependent fashion, whereas bDMARDs do not have the same impact.[32 40] Recently published US guidelines on the perioperative management of antirheumatic medication in patients with RA undergoing THA/TKA recommend withholding bDMARDs before and after surgery, whereas glucocorticoids can be continued in daily doses but should not be given in 'stress-doses'.[41]

Our finding of an increased 1-year mortality in patients with RA versus patients with OA is in agreement with an Australian study.[17] The increased mortality rates in years 1–10 compared with year 0–1 after surgery in our study suggest disease-specific rather than surgery-induced mortality. This does, however, not explain why other studies have reported similar or even decreased short-term (<90 days) risk of death among patients with RA compared with other THA/TKA recipients.[7 8 36 42–44] bDMARD exposure was not associated with increased 1-year mortality risk in our study, whereas glucocorticoid treatment proved a risk factor in a dose-dependent manner, which to our knowledge is a novel finding.

Our study has several strengths of which the most important is the nationwide set-up utilising registers with no loss to follow-up. We adjusted for several important confounders in our analysis of the impact of bDMARD treatment, including disease-specific factors such as DAS28-CRP and glucocorticoid treatment.

However, our study also has some important limitations: the number of events in bDMARD analyses was low thereby decreasing the statistical power. Also, we cannot exclude some degree of misclassification in DMARD and glucocorticoid treatment episodes: currently, there is no validation study of medication data from DANBIO, which is also the reason we did not investigate the risk with preoperative pausing versus continued bDMARD treatment. Furthermore, PJI can be difficult to diagnose, and this carries over to the (lack of) registration in arthroplasty and healthcare registers with sometimes less than optimal PPVs, although we have no reason to believe this problem should be particularly biased in one patient group over another. Lastly, we cannot rule out that the increased risk of death and PJIs among patients with RA and particularly glucocorticoid-treated patients with RA could be due to residual confounding although we believe the risk of this being the case is minimal.

In conclusion, patients with RA had increased 1-year risks of PJI and death and decreased risk of long-term revision compared with patients with OA following THA/TKA. bDMARD treatment within 90 days preceding surgery was not associated with statistically significant increased risk of revision, PJI nor death. On the contrary, glucocorticoid treatment was a strong risk factor for 1-year mortality and increased DAS28 was independently associated with 1-year PJI risk.

Author affiliations
[1]Department of Rheumatology, Gentofte Hospital, Center for Rheumatology and Spine Diseases, Rigshospitalet, Copenhagen, Denmark
[2]Bispebjerg and Frederiksberg Hospital, The Parker Institute, Frederiksberg, Denmark
[3]Department of Orthopaedic Surgery and Traumatology, Odense University Hospital, Odense, Denmark
[4]Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[5]Department of Orthopaedic Surgery, Copenhagen University Hospital Herlev-Gentofte, Gentofte, Denmark
[6]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[7]Department of Rheumatology, Odense University Hospital, Odense, Denmark

Acknowledgements We would like to thank all the departments of rheumatology in Denmark for reporting to the DANBIO Register, and equally so all departments of orthopaedic surgery for their devotion to registering in DHR and DKR.

Contributors RLC and LD had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: RLC, LD, AO, LEK and SO. Acquisition, analysis and interpretation of data: all authors. Drafting of the manuscript: RLC. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: RLC and LD. Study supervision: LD, AO, LEK and SO.

Funding The study was funded by The Danish Rheumatism Association, The Bjarne Jensen Foundation, the Oak Foundation and the Danish Council for Independent Research.

Competing interests PH has received speaking fees from Celgene and UCB outside the present work. LEK has received fees for speaking and/or consultancy from Pfizer, AbbVie, Amgen, UCB, Celgene, BMS, Biogen, Sanofi, MSD, Novartis, Eli Lilly and Janssen Pharmaceuticals. LD has received speaking fees from MSD and UCB outside the present work.

Ethics approval According to Danish legislation, publication of data from registers and databases does not require patient consent or ethics approval. Approval was given by the Danish Data Protection Agency (GEH-2014-043, I-Suite: 03166).

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Singh JA, Cameron C, Noorbaloochi S, *et al*. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. *Lancet* 2015;386:258–65.
2 Goodman SM, Menon I, Christos PJ, *et al*. Management of perioperative tumor necrosis-a inhibitors in rheumatoid arthritis undergoing arthroplasty: A systematic review and meta-analysis. *Rheumatol* 2015;53:1–10.
3 Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med* 2004;351:1645–54.
4 Bozic KJ, Kamath AF, Ong K, *et al*. Comparative epidemiology of revision arthroplasty: Failed tha poses greater clinical and economic burdens than failed tka. *Clin Orthop Relat Res* 2015;473:2131–8.
5 Schnaser EA, Browne JA, Padgett DE, *et al*. Perioperative complications in patients with inflammatory arthropathy undergoing total knee arthroplasty. *J Arthroplasty* 2015;30:76–80.
6 Schnaser EA, Browne JA, Padgett DE, *et al*. Perioperative complications in patients with inflammatory arthropathy Undergoing total hip arthroplasty. *J Arthroplasty* 2016;31:2286–90.
7 Ravi B, Croxford R, Hollands S, *et al*. Increased risk of complications following total joint arthroplasty in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2014;66:254–63.
8 Ravi B, Escott B, Shah PS, *et al*. A systematic review and meta-analysis comparing complications following total joint arthroplasty for rheumatoid arthritis versus for osteoarthritis. *Arthritis Rheum* 2012;64:3839–49.
9 Bozic KJ, Kurtz SM, Lau E, *et al*. The epidemiology of revision total hip arthroplasty in the United States. *J Bone Joint Surg Am* 2009;91:128–33.
10 Cancienne JM, Werner BC, Browne JA. Complications of primary total knee arthroplasty among patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and osteoarthritis. *J Am Acad Orthop Surg* 2016;24:863–8.
11 Schrama JC, Fenstad AM, Dale H, *et al*. Increased risk of revision for infection in rheumatoid arthritis patients with total hip replacements A study of 390. *Nordic Arthroplasty Regis- ter Association* 2015;86:1–7.
12 Rud-Sørensen C, Pedersen AB, Johnsen SP, *et al*. Survival of primary total hip arthroplasty in rheumatoid arthritis patients. *Acta Orthop* 2010;81:60–5.
13 Pieringer H, Stuby U, Biesenbach G. Patients with rheumatoid arthritis undergoing surgery: how should we deal with antirheumatic treatment? *Semin Arthritis Rheum* 2007;36:278–86.
14 Tada M, Inui K, Sugioka Y, *et al*. Delayed wound healing and postoperative surgical site infections in patients with rheumatoid arthritis treated with or without biological disease-modifying antirheumatic drugs. *Clin Rheumatol* 2016;35:1475–81.
15 George MD, Baker JF, Yenchih Hsu J, *et al*. Perioperative timing of infliximab and the risk of serious infection after elective hip and knee arthroplasty. *Arthritis Care Res* 2017.
16 Soohoo NF, Farng E, Lieberman JR, *et al*. Factors that predict short-term complication rates after total hip arthroplasty. *Clin Orthop Relat Res* 2010;468:2363–71.
17 Tropea J, Brand CA, Bohensky M, *et al*. Myocardial infarction and mortality following joint surgery in patients with rheumatoid arthritis: a retrospective cohort study. *Arthritis Res Ther* 2016;18:69.
18 Von EE, Altman DG, Egger M, *et al*. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Br Med J* 2007;335:19–22.
19 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–9.
20 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39:30–3.
21 Ibfelt EH, Jensen DV, Hetland ML. The Danish nationwide clinical register for patients with rheumatoid arthritis: DANBIO. *Clin Epidemiol* 2016;8:737–42.
22 Gundtoft PH, Varnum C, Pedersen AB, *et al*. The danish hip arthroplasty register. *Clin Epidemiol* 2016;8:509–14.
23 Gundtoft PH, Overgaard S, Schønheyder HC, *et al*. The "true" incidence of surgically treated deep prosthetic joint infection after 32,896 primary total hip arthroplasties: a prospective cohort study. *Acta Orthop* 2015;86:326–34.
24 Pedersen AB, Mehnert F, Odgaard A, *et al*. Existing data sources for clinical epidemiology: The Danish Knee Arthroplasty Register. *Clin Epidemiol* 2012;4:125–35.
25 Pedersen M, Klarlund M, Jacobsen S, *et al*. Validity of rheumatoid arthritis diagnoses in the Danish National Patient Registry. *Eur J Epidemiol* 2004;19:1097–103.
26 Gundtoft PH, Pedersen AB, Schønheyder HC, *et al*. Validation of the diagnosis 'prosthetic joint infection' in the Danish Hip Arthroplasty Register. *Bone Joint J* 2016;98-B:320–5.
27 Lange J, Pedersen AB, Troelsen A, *et al*. Do hip prosthesis related infection codes in administrative discharge registers correctly classify periprosthetic hip joint infection? *Hip Int* 2015;25:568–73.
28 Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health* 1989;79:340–9.
29 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;30:377–99.
30 R: A language and environment for statistical computing. R Found. Stat. Comput. 2008.
31 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
32 Zink A, Manger B, Kaufmann J, *et al*. Evaluation of the RABBIT Risk Score for serious infections. *Ann Rheum Dis* 2014;73:1673–6.
33 Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. *Nat Rev Rheumatol* 2012;8:656–64.
34 Ringen HO, Dagfinrud H, Mowinckel P, *et al*. Patients with rheumatoid arthritis report greater physical functional deterioration in lower limbs compared to upper limbs over 10 years. *Scand J Rheumatol* 2008;37:255–9.
35 Bongartz T, Halligan CS, Osmon DR, *et al*. Incidence and risk factors of prosthetic joint infection after total hip or knee replacement in patients with rheumatoid arthritis. *Arthritis Rheum* 2008;59:1713–20.
36 Schnaser EA, Browne JA, Padgett DE, *et al*. Perioperative complications in patients with inflammatory arthropathy undergoing total knee arthroplasty. *J Arthroplasty* 2015;30:76–80.
37 Jämsen E, Huhtala H, Puolakka T, *et al*. Risk factors for infection after knee arthroplasty. A register-based analysis of 43,149 cases. *J Bone Joint Surg Am* 2009;91:38–47.
38 Huotari K, Peltola M, Jämsen E. The incidence of late prosthetic joint infections: a registry-based study of 112,708 primary hip and knee replacements. *Acta Orthop* 2015;86:321–5.
39 Schrama JC, Espehaug B, Hallan G, *et al*. Risk of revision for infection in primary total hip and knee arthroplasty in patients with rheumatoid arthritis compared with osteoarthritis: a prospective, population-based study on 108,786 hip and knee joint arthroplasties from the Norwegian Arthroplasty Register. *Arthritis Care Res* 2010;62:473–9.
40 Crowson CS, Hoganson DD, Fitz-Gibbon PD, *et al*. Development and validation of a risk score for serious infection in patients with rheumatoid arthritis. *Arthritis Rheum* 2012;64:2847–55.
41 Goodman SM, Springer B, Guyatt G, *et al*. 2017 American college of rheumatology/ american association of hip and knee surgeons guideline for the perioperative management of antirheumatic medication in patients with rheumatic diseases undergoing elective total hip or total knee arthroplasty. *Arthritis Care Res* 2017;69:1111–24.
42 Michaud K, Fehringer EV, Garvin K, *et al*. Rheumatoid arthritis patients are not at increased risk for 30-day cardiovascular events, infections, or mortality after total joint arthroplasty. *Arthritis Res Ther* 2013;15:R195.
43 Stundner O, Danninger T, Chiu YL, *et al*. Rheumatoid arthritis vs osteoarthritis in patients receiving total knee arthroplasty: perioperative outcomes. *J Arthroplasty* 2014;29:308–13.
44 Stundner O, Chiu YL, Sun X, *et al*. Perioperative outcomes in patients with rheumatoid versus osteoarthritis for total hip arthroplasty: a population-based study. *Clin Exp Rheumatol* 2013;31:31889–95.

OPEN ACCESS

CONCISE REPORT

Testing treat-to-target outcomes with initial methotrexate monotherapy compared with initial tumour necrosis factor inhibitor (adalimumab) plus methotrexate in early rheumatoid arthritis

Arthur Kavanaugh,[1] Ronald F van Vollenhoven,[2] Roy Fleischmann,[3] Paul Emery,[4,5] Iain Sainsbury,[6] Stefan Florentinus,[6] Su Chen,[6] Benoît Guérette,[6] Hartmut Kupper,[7] Josef S Smolen[8]

Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-211871).

For numbered affiliations see end of article.

Correspondence to
Professor Arthur Kavanaugh, Division of Rheumatology, Allergy, and Immunology, School of Medicine, University of California at San Diego, La Jolla, California 92093, USA; akavanaugh@ucsd.edu

Received 31 May 2017
Revised 30 October 2017
Accepted 3 November 2017
Published Online First 4 December 2017

ABSTRACT

Objectives To compare responses in patients with early rheumatoid arthritis (RA) initially treated with the tumour necrosis factor inhibitor (TNFi) adalimumab+methotrexate (MTX) versus MTX monotherapy who may have continued receiving MTX or switched to adalimumab rescue therapy after inadequate response to MTX.

Methods OPTIMA enrolled MTX-naive patients with active RA for <1 year. This post hoc analysis determined the proportion of patients, stratified by initial treatment, who achieved 28-joint modified Disease Activity Score based on C reactive protein <3.2, normal function and/or no radiographic progression at weeks 26, 52 and 78.

Results Significantly greater proportions of patients initially treated with adalimumab+MTX (n=466) compared with MTX monotherapy (n=460) achieved good clinical (53% vs 30%), functional (45% vs 33%) and radiographic (87% vs 72%) outcomes at week 26. From weeks 26 to 78, adalimumab rescue patients achieved similar clinical and functional outcomes versus patients initially treated with adalimumab+MTX. However, significantly more patients initially treated with adalimumab+MTX had no radiographic progression at weeks 52 and 78 versus patients initially treated with MTX (both timepoints: 86% vs 72%).

Conclusions In early RA, starting with MTX monotherapy and adding TNFi after 26 weeks yields similar longer term clinical results as starting with TNFi+MTX combination therapy but allows a small but significant accrual of radiographic damage.

INTRODUCTION

The European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) recommend clinical remission or low disease activity (LDA) if remission is unlikely to be obtained, as the treatment goal for rheumatoid arthritis (RA).[1 2] Conventional synthetic disease-modifying antirheumatic drugs (DMARDs), particularly methotrexate (MTX), are recommended as part of an initial treatment strategy. If disease activity has not improved at 3 months, or the clinical target is not attained within 6 months and the patient has unfavourable prognostic markers, addition of a biological DMARD (bDMARD), such as a tumour necrosis factor inhibitor (TNFi), is recommended.[1 2]

This analysis evaluated the treat-to-target strategy by assessing whether patients with early RA who started on MTX monotherapy, followed by addition of adalimumab on treatment failure, had a similar or worse outcomes compared with patients who started on adalimumab+MTX combination therapy.

METHODS

Study design

OPTIMA was a 78-week, randomised, double-blind, phase 4, two-period study.[3 4] In period 1, patients received MTX monotherapy weekly or adalimumab 40 mg every other week plus MTX weekly for 26 weeks.[3] The protocol defined stable LDA as 28-joint modified Disease Activity Score based on C reactive protein (DAS28(CRP)) <3.2 at weeks 22 and 26. In period 2, patients with stable LDA continued MTX monotherapy or were rerandomised to adalimumab+MTX continuation or adalimumab withdrawal (MTX only).[4] Patients who did not achieve stable LDA in period 1 continued open-label MTX+adalimumab (adalimumab carry-on) or received open-label adalimumab added to MTX monotherapy (adalimumab rescue). All patients remained blinded to their initial treatment allocation in period 1.[4]

Post hoc populations

A 'merged adalimumab continuation' group (including the ADA continuation arm, adjusted with a scaling factor based on the total number of patients in the adalimumab continuation and adalimumab withdrawal arms, so that both arms contributed equally) was combined with the adalimumab carry-on arm, comprising the total population randomised to adalimumab+MTX at baseline (online supplementary figure 1). The MTX monotherapy and adalimumab rescue arms were combined. These two main groupings allowed comparison of the validity of the EULAR and ACR recommendations of starting with MTX monotherapy followed by addition of a TNFi in patients who do not achieve the treatment target versus starting with TNFi+MTX.

To cite: Kavanaugh A, van Vollenhoven RF, Fleischmann R, *et al*. *Ann Rheum Dis* 2018;**77**:289–292.

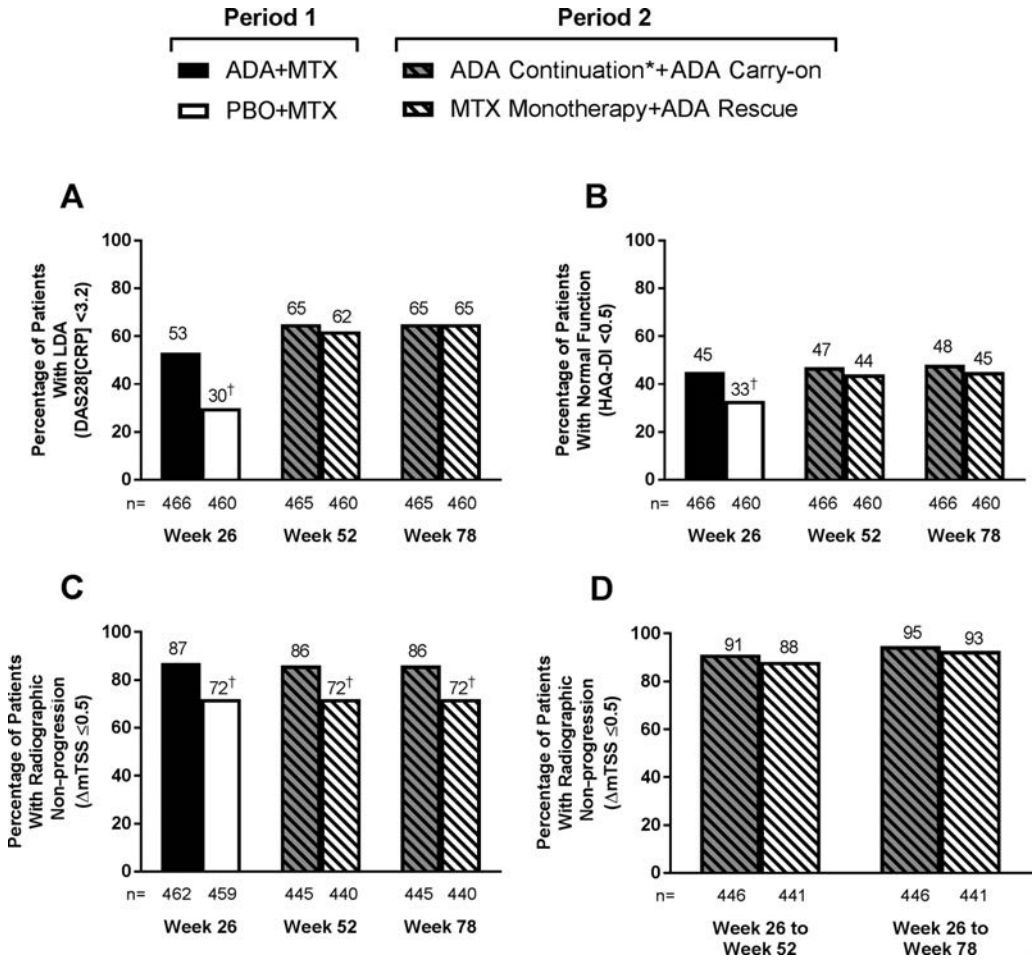


Figure 1 Percentage of patients with clinical, functional and radiographic outcomes stratified by initial treatment regimen. (A) LDA based on DAS28(CRP) <3.2 at weeks 26, 52 and 78. (B) Normal function based on HAQ-DI <0.5 at weeks 26, 52 and 78. (C) Radiographic non-progression based on ΔmTSS ≤0.5 at weeks 26, 52 and 78. (D) Radiographic nonprogression based on ΔmTSS ≤0.5 from week 26 to 52 and from week 26 to 78. *This analysis group included the ADA continuation arm (n=105) and, after scaling to yield a proportional equivalent number of patients, the ADA withdrawal arm (n=102). †P<0.001, χ^2 test. Missing DAS28(CRP) and HAQ-DI data were imputed using last observation carried forward; missing ΔmTSS data were imputed using multiple imputation. ADA, adalimumab; CRP, C reactive protein; DAS28, 28-joint modified Disease Activity Score; HAQ-DI, Disability Index of the Health Assessment Questionnaire; LDA, low disease activity; mTSS, modified total Sharp score; MTX, methotrexate; PBO, placebo.

Efficacy assessments

The main assessments were the proportion of patients who achieved DAS28(CRP) <3.2, normal function and no radiographic progression at weeks 52 and 78. Normal function was defined as Disability Index of the Health Assessment Questionnaire (HAQ-DI) <0.5 and radiographic non-progression as change in modified total Sharp score (ΔmTSS) ≤0.5. We also assessed Boolean-based remission,[5] Simplified Disease Activity Index (SDAI) remission (≤3.3), response rates for 20%/50%/70% improvements in ACR criteria and patient-reported outcomes (global assessment, pain, Functional Assessment of Chronic Illness Therapy and EuroQoL-5 dimensions).

Statistical analyses

Outcomes were assessed using the last observation carried forward method, except radiographic analyses used multiple imputation (missing values imputed in 10 steps, Markov chain Monte Carlo method).[6] Categorical outcomes were compared using the Pearson χ^2 test[4] and continuous outcomes using one-sample or two-sample t-tests.

RESULTS

As reported previously,[3] a significantly greater proportion of patients receiving adalimumab+MTX, compared with those starting on MTX only, achieved LDA, normal function and radiographic non-progression at week 26. However, after therapy adjustment at week 26 in patients who failed to attain LDA, the proportions achieving LDA at weeks 52 and 78 and normal function were similar between the groups (figure 1A,B). Results were independent of glucocorticoid use (online supplementary figure 2). Moreover, the proportion of patients with radiographic non-progression (from week 0) remained stable from weeks 26 to 52 and 78, indicating that as soon as adalimumab rescue therapy began at week 26, progression of joint damage stopped (figure 1C). Likewise, the proportion of patients with radiographic non-progression from week 26 ('reset' baseline) to week 52 or 78 was similar between the groups (figure 1D). Moreover, the proportion of MTX monotherapy responders without radiographic progression at week 26 remained stable (ΔmTSS ≤0.5: 89/109 (81.7%) at week 52, 85/109 (78.0%) at week 78). Although significantly greater proportions of patients starting with adalimumab+MTX also achieved Boolean-based remission at weeks 26 and 52 and SDAI remission at week 26 versus

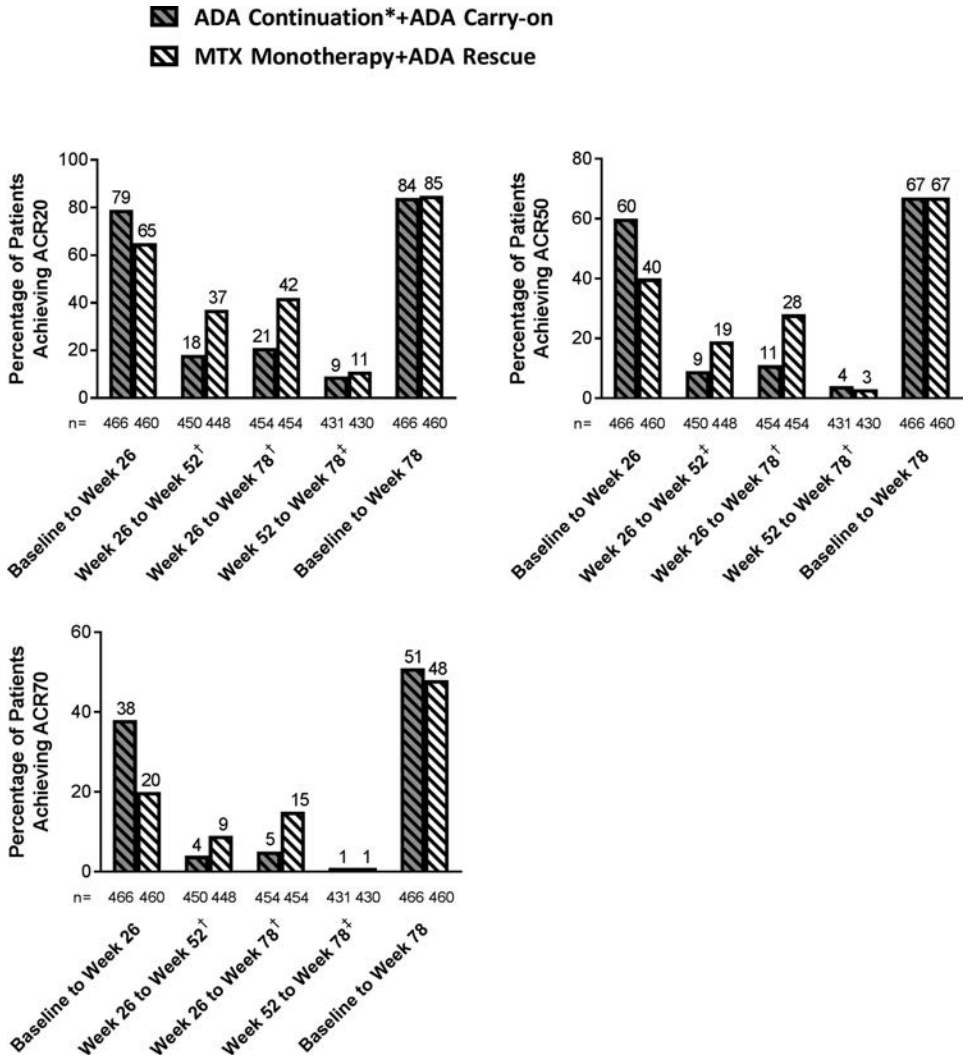


Figure 2 Response rates for patients achieving (A) 20%, (B) 50% and (C) 70% improvement in ACR criteria over the course of 78 weeks. *This analysis group included the ADA continuation arm (n=105) and, after scaling to yield a proportional equivalent number of patients, the ADA withdrawal arm (n=102). †Percentage improvement was assessed from week 26. ‡Percentage improvement was assessed from week 52. Missing data were imputed using last observation carried forward. ACR, American College of Rheumatology; ADA, adalimumab; MTX, methotrexate.

patients starting with MTX monotherapy, the differences were no longer significant subsequently (data not shown). Mean changes in clinical, functional and radiographic scores were significantly better in patients starting with adalimumab+MTX ($P<0.001$) from baseline to week 26, whereas mean changes (except radiographic scores) were significantly better in patients starting with MTX monotherapy ($P<0.001$) from week 26 to weeks 52 and 78 (ie, after possible addition of adalimumab; data not shown). Mean changes in patient-reported outcomes from week 26 to weeks 52 and 78 were similar in the two groups (data not shown).

ACR response rates from baseline to week 26 were higher on starting with adalimumab+MTX versus starting with MTX monotherapy, whereas in those starting with MTX monotherapy, the ACR rates were higher from week 26 to weeks 52 and 78 (figure 2). However, response rates were similar between groups from week 52 to week 78 or baseline to week 78.

DISCUSSION

This post hoc analysis of patients with early, active RA (disease duration: ~4 months[3]) compared 78-week outcomes in patients initially treated with MTX monotherapy, followed by addition of adalimumab if treatment target was not achieved, versus patients initially treated with adalimumab+MTX combination therapy. Patients initially treated with MTX monotherapy had similar clinical, functional and patient-reported outcomes at weeks 52 and 78 as patients initially treated with adalimumab+MTX. Although initial adalimumab+MTX combination therapy resulted in minimally superior radiographic outcomes at a group level compared with initial MTX monotherapy, these mean differences were not deemed clinically relevant because, per an established formula, this 1-point difference on the radiographic scale translates to a negligible extent of irreversible functional impairment at the group level (0.01 HAQ points).[7] Also, patients starting with adalimumab+MTX had higher ACR response rates in period 1 than patients starting with MTX monotherapy, but this pattern was reversed at week 52 when the baseline was 'reset' to week 26, so overall ACR response rates were similar by week 78. Thus, at a population level, starting with MTX monotherapy followed by addition of adalimumab in patients with early RA who did not respond to MTX within 6 months conveyed almost identical clinical, functional and quality of life (but not radiological) results at weeks 52 and/or 78 versus starting with adalimumab+MTX.

EULAR and ACR recommend starting with MTX monotherapy or MTX+glucocorticoids[1 2 8] but not with a bDMARD+MTX, in all patients with RA. In patients who do not achieve a treatment target of at least LDA and who have unfavourable prognostic factors (as in OPTIMA), adding a bDMARD is recommended. Our data fully validate this treat-to-target strategy[2] by showing that the overall population of patients starting on MTX monotherapy, over time, fared as well in clinical, functional and structural respects as those starting on adalimumab+MTX. Furthermore, among those starting on MTX monotherapy, 24% achieved stable LDA at week 26,[3] with little or no radiographic progression and mostly normative physical function thereafter; thus, the treat-to-target strategy allows for a good outcome without the need for a bDMARD, despite negative prognostic factors, and prevents overtreatment of one in four patients with active RA. Overall, by applying this strategy, approximately two of three patients with early RA achieve LDA or remission, the major therapeutic targets, within 1 year with essentially no or minimal joint damage.

To our knowledge, no previous study has addressed whether rapid addition of TNFi after MTX failure leads to different disease outcomes compared with an initial combination of TNFi+MTX. A further strength is the prospective design of this study. Limitations include the inherent bias of post hoc analyses and that the target was defined a priori as DAS28(CRP) <3.2, rather than a more stringent response. Patients were also not allowed alterations in glucocorticoids as recommended in treatment guidelines.[1 2 8] Additionally, all patients who failed to achieve a clinical target received adalimumab and MTX, without comparisons with other rescue treatment options (eg, triple DMARD therapy and another bDMARD). The adalimumab+MTX population was not treated-to-target, unlike the MTX monotherapy population, since no treatment adjustment was made in patients who did not achieve stable LDA with adalimumab+MTX at week 26. Nonetheless, many adalimumab+MTX patients had further clinical/functional improvements and maintained the halt of radiographic progression. Furthermore, treatment was switched to MTX monotherapy in a subset of patients starting with adalimumab+MTX who had LDA at weeks 22 and 26; no equivalent removal of a therapeutic component was allowed in patients starting with MTX monotherapy who achieved stable LDA. Finally, rescue therapy was open label, which could have biased patient responses, particularly for the more subjective endpoints (eg, HAQ-DI); however, the initial treatment allocation remained blinded throughout the trial.

CONCLUSIONS

Consistent with current treatment recommendations, starting with MTX monotherapy and optimising treatment by adding adalimumab after treatment failure at 26 weeks allowed patients with early RA to achieve comparable long-term clinical, functional and disease activity outcomes with patients who started with initial adalimumab+MTX combination therapy. This strategy also prevented potential overtreatment of approximately 25% of patients with early RA.

Author affiliations
[1]Division of Rheumatology, Allergy and Immunology, School of Medicine, University of California at San Diego, La Jolla, California, USA
[2]Amsterdam Rheumatology and Immunology Center ARC, Amsterdam, The Netherlands
[3]University of Texas Southwestern Medical Center, Metroplex Clinical Research Center, Dallas, Texas, USA
[4]Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Leeds, UK
[5]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[6]AbbVie Inc., North Chicago, Illinois, USA
[7]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany
[8]Medical University of Vienna and Hietzing Hospital, Vienna, Austria

Acknowledgements Medical writing support was provided by Amanda Sheldon, PhD, Patrick Little, PhD, Katherine Groschwitz, PhD, Maria Hovenden, PhD, and Michael J. Theisen, PhD, of Complete Publication Solutions, LLC; this support was funded by AbbVie Inc. AbbVie and the authors would like to thank the patients who participated in the clinical trial and all study investigators for their contributions.

Contributors All authors have contributed to the work and approve the presented findings.

Funding AbbVie sponsored the study (OPTIMA; M06-810; NCT00420927) and analysis; contributed to their design and was involved in the collection, analysis and interpretation of the data. AbbVie was involved in the writing, review and approval of the manuscript.

Competing interests AK has provided remunerated expert advice to and received grant/research support for his institution from AbbVie. RFvV has received grants and research support from AbbVie, Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Roche and UCB, and consulting fees and honoraria from AbbVie, AstraZeneca, Biotest, Bristol-Myers Squibb, Celgene, Crescendo, GlaxoSmithKline, Centocor-Janssen, Lilly, Merck, Novartis, Pfizer, Roche, UCB and Vertex. RF provided remunerated expert advice to and received grant support from AbbVie. PE has received research grants and/or consulting fees from AbbVie, Bristol-Myers Squibb, Lilly, Merck, Novartis, Pfizer, Roche, Sandoz and UCB. SF, IS and SC are employees of AbbVie and may hold stock or stock options. BG is a former employee of AbbVie and may hold stock or stock options. HK is an employee of AbbVie Deutschland GmbH & Co KG and may hold stock or stock options. JSS has provided remunerated expert advice to and received grant/research support for his institution from AbbVie.

Ethics approval A central institutional review board or independent ethics committee approved the study at each of the 161 study sites.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Singh JA, Saag KG, Bridges SL Jr, *et al*. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2016;68:1–26.
2 Smolen JS, Landewé R, Bijlsma J, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017;76:960–77.
3 Kavanaugh A, Fleischmann RM, Emery P, *et al*. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. *Ann Rheum Dis* 2013;72:64–71.
4 Smolen JS, Emery P, Fleischmann R, *et al*. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. *Lancet* 2014;383:321–32.
5 Bykerk VP, Massarotti EM. The new ACR/EULAR remission criteria: rationale for developing new criteria for remission. *Rheumatology* 2012;51(suppl 6):vi16–vi20.
6 Baron G, Ravaud P, Samson A, *et al*. Missing data in randomized controlled trials of rheumatoid arthritis with radiographic outcomes: a simulation study. *Arthritis Rheum* 2008;59:25–31.
7 Smolen JS, Aletaha D, Grisar JC, *et al*. Estimation of a numerical value for joint damage-related physical disability in rheumatoid arthritis clinical trials. *Ann Rheum Dis* 2010;69:1058–64.
8 Smolen JS, Landewé R, Breedveld FC, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73:492–509.

EXTENDED REPORT

Low-dose CT detects more progression of bone formation in comparison to conventional radiography in patients with ankylosing spondylitis: results from the SIAS cohort

Anoek de Koning,[1] Freek de Bruin,[2] Rosaline van den Berg,[1] Sofia Ramiro,[1] Xenofon Baraliakos,[3] Juergen Braun,[3] Floris A van Gaalen,[1] Monique Reijnierse,[2] Désirée van der Heijde[1]

Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-211989).

[1]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[2]Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands
[3]Department of Rheumatology, Rheumazentrum Ruhrgebiet Herne, Herne, Germany

Correspondence to
Professor Désirée van der Heijde, Department of Rheumatology, Leiden University Medical Center, 2300 RC Leiden, The Netherlands; mail@dvanderheijde.nl

Received 28 June 2017
Revised 17 October 2017
Accepted 29 October 2017
Published Online First 10 November 2017

ABSTRACT

Objectives To compare the CT Syndesmophyte Score (CTSS) for low-dose CT (ldCT) with the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) for conventional radiographs (CR) in patients with ankylosing spondylitis (AS).

Methods Patients with AS in the Sensitive Imaging in Ankylosing Spondylitis cohort had lateral cervical and lumbar spine CR and whole spine ldCT at baseline and 2 years. CR and ldCT images were scored by two readers, paired by patient, blinded to time order, per imaging modality. For the total score analysis, we used average scores of readers per corner on CR or quadrant on ldCT. For the syndesmophyte analysis we used individual reader and consensus scores, regarding new or growing syndesmophyte at the same corner/quadrant.

Results 50 patients were included in the syndesmophyte analysis and 37 in the total score analysis. Mean (SD) status scores for mSASSS (range 0–72) and CTSS (range 0–552) at baseline were 17.9 (13.8) and 161.6 (126.6), and mean progression was 2.4 (3.8) and 17.9 (22.1). Three times as many patients showed new or growing syndesmophytes at ≥3 quadrants on ldCT compared with ≥3 corners on CR for individual readers; for consensus this increased to five times. In 50 patients, 36 new or growing syndesmophytes are seen on CR compared with 151 on ldCT, most being found in the thoracic spine.

Conclusions ldCT, covering the whole spine, detects more progression in the form of new and growing syndesmophytes in patients with AS compared with CR, which is limited to the cervical and lumbar spine. Most progression occurred in the thoracic spine.

INTRODUCTION

Ankylosing spondylitis (AS) is a disease with progressive structural damage of the spine, mainly characterised by the development of syndesmophytes, which is associated with impairment of spinal mobility and functional disability.[1–3] Currently, structural damage is assessed on conventional radiographs (CR), using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).[4] In this score, lateral CRs of the cervical and lumbar spine are assessed for new bone formation, as well as for erosions, sclerosis and squaring. This method has a scoring range of 0–72, with a mean progression score over 2 years of 2.1 if scored with known chronology and of 1.0 if scored without known chronology.[5] The shortest period to reliably assess progression using the mSASSS is 2 years, which limits the applicability of this method in research (eg, medication trials).[6]

Due to technological advances, it is now possible to perform CT of the spine with the relatively low radiation dose of 4 mSv (low-dose CT (ldCT)).[7] With ldCT it is possible to assess the entire vertebral column, thus including the thoracic spine, which doubles the number of available vertebrae. It is known both from CR and MRI that many abnormalities are seen in the (lower) thoracic spine.[8] Moreover, on ldCT vertebrae can be viewed from multiple angles and without overprojection. These advantages of ldCT could make it a more sensitive method for the assessment of radiographical progression in AS and lead to a reliable measurement of progression over a period shorter than 2 years. This would make research in AS, with structural damage as an outcome, more feasible.

Recently, the CT Syndesmophyte Score (CTSS) for the analysis of bone proliferation has been developed for ldCT.[7] This method has been shown to have good inter-reader reliability and sensitivity to pick up changes. The next step in the validation process is the comparison of the CTSS and the mSASSS for the assessment of structural progression in AS.

METHODS

Study population

For this study data from the Sensitive Imaging in Ankylosing Spondylitis (SIAS) cohort were used. This is an observational cohort including 60 patients with a diagnosis of AS and fulfilling the modified New York criteria from the Netherlands and Germany.[9] The follow-up period was 2 years. Inclusion criteria were age 18 years or older, at least one syndesmophyte in either the cervical or lumbar spine on lateral CR, and at least one inflammatory lesion on MRI of the whole spine. All treatments were allowed according to the treating rheumatologist. Exclusion criteria were >18 vertebral corners (VCs) affected by syndesmophytes in the cervical and lumbar spine combined, circumstances

To cite: de Koning A, de Bruin F, van den Berg R, *et al*. *Ann Rheum Dis* 2018;**77**:293–299.

Table 1 Description of the mSASSS and CT scoring methods

	mSASSS	CTSS
Spinal segments assessed		
Cervical spine	Lower border of C2 to upper border of T1	Lower border of C2 to upper border of T1
Thoracic spine	Not included	Lower border of T1 to upper border of T12
Lumbar spine	Lower border of T12 to S1	Lower border of T12 to S1
Range of scoring system	0–72	0–552
Sites per vertebral endplate		
Assessment at	Anterior corner	4 quadrants
Scoring grades		
0	No abnormalities	No abnormalities
1	Erosion, sclerosis, squaring	Syndesmophyte <50% of IDS
2	Syndesmophyte	Syndesmophyte ≥50% of IDS but not bridging
3	Bridging syndesmophyte	Bridging syndesmophyte
Definitions of syndesmophytes		
New	Score 0, 1→2, 3	Score 0→1, 2, 3
Growth	Score 2→3	Score 1→2, 3 or 2→3

C, cervical; CTSS, CT Syndesmophyte Score; IDS, intervertebral disc space; L, lumbar; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; S, sacral; T, thoracic.

that would invalidate informed consent or limit the ability of the patient to comply with protocol requirements, routine MRI contraindications and pregnancy. Clinical data and MRI of the whole spine were collected at baseline, 1 and 2 years. Lateral CR of the cervical and lumbar spine and ldCT of the whole spine with coronal and sagittal reconstructed images were obtained at baseline and 2 years.[7] For the present study patients were included if CR and ldCT were present at baseline and 2 years. The study fulfilled the Good Clinical Practice guidelines. Before inclusion, written informed consent was obtained from all patients.

Scoring methods

The two scoring methods are presented in table 1. For CR this was the mSASSS, scoring two anterior VCs per vertebral unit (VU) of the cervical and lumbar spine on a lateral view (12 VUs in total).[4] The total score ranges from 0 to 72. For ldCT, the anterior and posterior quadrants of the cervical, thoracic and lumbar spine were scored in coronal and sagittal planes (23 VUs in total), scoring eight quadrants per VU.[7] The total score ranges from 0 to 552. In order to compare bone formation between CR and ldCT, levels were defined per VU. Level 1 refers to the upper border of a VU (which is the lower half of the vertebra) and level 2 to the lower border of the VU (which is the upper half of the vertebra). For CR every level incorporates one corner, for ldCT every level incorporates four quadrants.

CR and ldCT were scored independently in separate sessions by two trained readers (RvdB and FdB). Images for the two time points were paired by patient, blinded to time order, patient information and the other imaging technique. LdCT reconstructed images were performed by the CT technicians in the sagittal and coronal planes.

Comparison of mSASSS with CTSS

Average scores of both readers per VC for CR and per quadrant for ldCT were used. If one reader indicated a VC or quadrant as missing, the score of the other reader was used. Patients were only included if ≥75% of the VCs or quadrants per spinal segment (ie, cervical, thoracic and lumbar) were present. For CR, this meant a maximum of three missing VCs for the cervical and lumbar spine separately. For ldCT, this meant a maximum of 12 missing quadrants for the cervical and lumbar spine separately and 22 for the thoracic spine. Missing scores, after applying the previous two rules, were imputed using a method previously described by Ramiro *et al*.[10] Briefly, if the 2-year status score was missing, the mean spinal segment progression score (ie, based on the present VCs/quadrants in the same segment) was added to the baseline status score of the same corner/quadrant and ensuring that a score of 3 (maximum score per VC/quadrant) would never be surpassed. Similarly, for baseline missing scores, the mean spinal segment progression score was subtracted from the 2-year VC/quadrant score ensuring that the minimum value possible was 0 and also ensuring 0 was considered for baseline when the same VC/quadrant had a score of 0 at 2 years. If a score was missing at both time points, the average spinal segment score per time point was used for that VC/quadrant for baseline, followed by the imputation of the mean segment progression to obtain the 2-year score, as previously explained. Progression scores were calculated by subtracting the baseline status score from the 2-year status score. This was done for the whole spine as well as per spinal segment. The net number of patients with progression above 0, 0.5 or the smallest detectable change (SDC) were calculated by subtracting the number of patients with a change score <0, <-0.5 or $<-$SDC from the number of patients with a change score >0, >0.5 or $>$SDC.

Comparison of syndesmophytes on CR and ldCT

For this analysis, there was no requirement regarding the minimum number of VCs or quadrants present. Scores from separate readers and a consensus score were used. Consensus was present if both readers agreed on a new or growing syndesmophyte at the same VC or quadrant. For the definitions of new or growing syndesmophytes for CR and ldCT, see table 1. The formation of new syndesmophytes and growth of syndesmophytes were compared per level. Therefore, a patient had four times the chance of showing a new or growing syndesmophyte per level on ldCT compared with CR. Three separate analyses were performed for this comparison. The first analysis compared the number of patients with syndesmophyte formation or growth per reader, and for the consensus score taking all levels together. The second analysis also focuses on the number of patients with syndesmophyte formation or growth; however, this is now analysed per level. The third analysis focuses on the number of new or growing syndesmophytes (and thus not of patients) per level based on the consensus score. The analyses were performed separately for newly formed syndesmophytes, for growth of syndesmophytes only, and for the combination of newly formed and growth of syndesmophytes.

Statistical analysis

Disease characteristics were assessed using descriptive statistics. Interobserver reliability was assessed for both CR and ldCT by Bland-Altman plots and SDC, and additional reliability assessments (eg, intraclass correlation coefficient (ICC)) have been presented in the manuscript on the development of the CTSS.[7 11] The SDC is the smallest change that can be detected beyond measurement error and was calculated as follows: $SDC = 1.96 \times SD_{diff}/(\sqrt{k} \times \sqrt{2})$.[12] SD is the standard deviation of the difference in progression scores between two readers, and k is the number of readers. Comparisons of the number of patients with new or growing syndesmophytes on CR versus ldCT per reader and for the consensus score are presented as a heatmap,

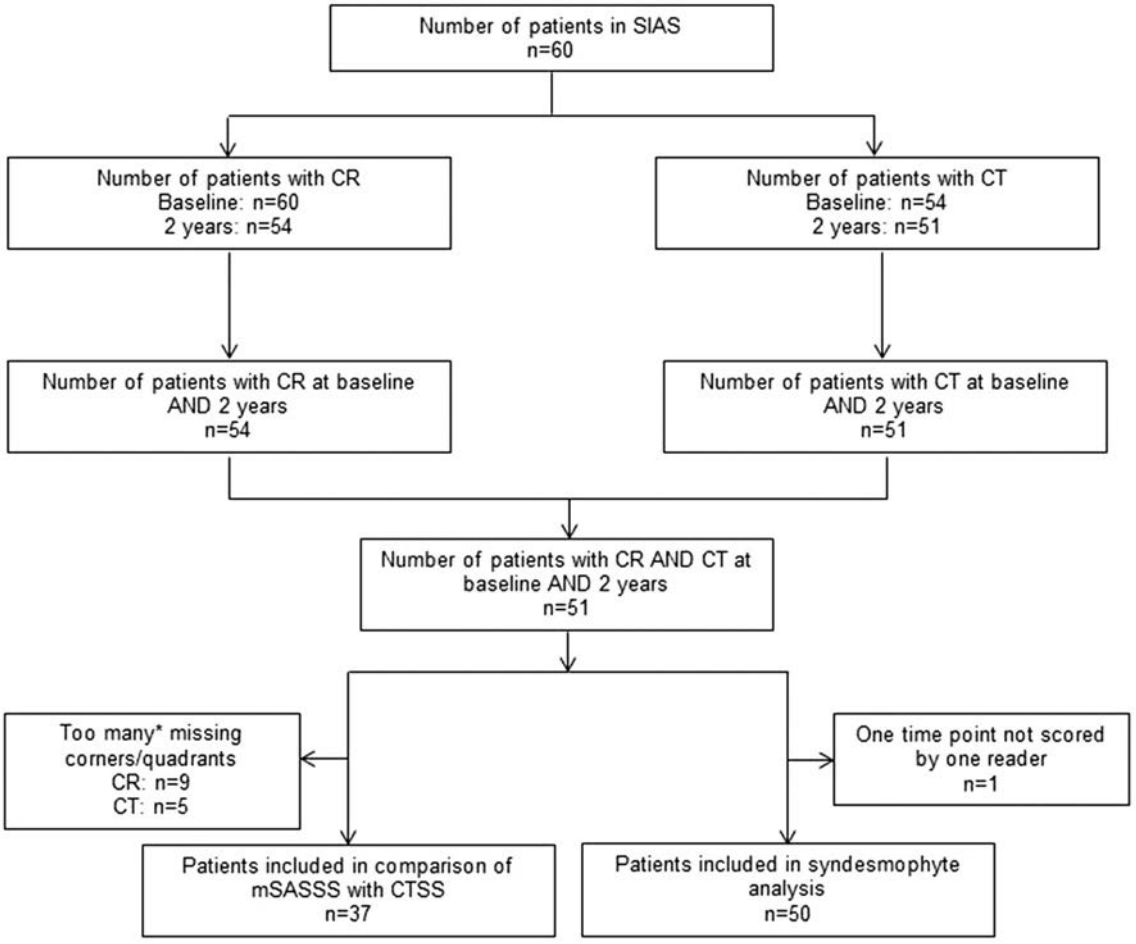


Figure 1 Flow chart for the analysis of syndesmophytes on CR and CT. *>25% of the corners/quadrants of the cervical thoracic or lumbar spine missing. CR, conventional radiography; CTSS, CT Syndesmophyte Score; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; SIAS, Sensitive Imaging in Ankylosing Spondylitis.

showing results of all individual spinal levels. In a similar way, the new and growing syndesmophytes are presented. The corresponding progression score of the mSASSS and CTSS per patient is presented by a double probability plot. All analyses were performed using STATA SE V.14.

RESULTS

Of the 60 patients in the cohort, a total of 51 had both CR and ldCT at baseline and 2 years (figure 1). Because of exclusion of patients due to missing VCs or quadrants, 37 patients were included in the comparison of mSASSS and CTSS. Reasons for these missing VCs on CR were the inability to score the lower four cervical VCs due to overprojection (n=6) or the absence of CR of either the cervical or lumbar spine (n=3). Reasons for the missing quadrants on ldCT were either bad quality of the ldCT (n=3) or missing cervical spine (n=2). In the comparison of syndesmophytes, 50 patients were included (figure 1).

Baseline demographics and clinical characteristics are summarised in online supplementary table 1. The following were the characteristics of the patients included in the syndesmophyte analysis: 84% male, mean age of 50 years (SD 9.8), 86% were human leukocyte antigen (HLA-)B27-positive, 38% had elevated C reactive protein, mean Ankylosing Spondylitis Disease Activity Score (ASDAS) was 2.5 (SD 1.2), 62% used non-steroidal anti-inflammatory drugs, 26% used disease-modifying antirheumatic drugs and 22% used tumour necrosis factor alpha blockers. For patients included in the comparison of mSASSS and CTSS, the characteristics were similar (see online supplementary table 1).

Comparison of mSASSS with CTSS

The mean mSASSS status score at baseline was 17.9 (SD 13.8) and the mean progression was 2.4 (SD 3.8). The mean CTSS status score at baseline was 161.7 (SD 126.6) and the mean progression was 17.9 (SD 22.1). The mean status and progression scores for all patients for whom the mSASSS (n=45) and CTSS (n=46) could be calculated were similar to the values of patients included in the analysis. Data for separate groups and spinal segments are presented in online supplementary table 2.

Bland-Altman plots of the progression scores for CR and ldCT showed that the data were homoscedastic; there was however a small systematic error for both CR and ldCT. Reader 2 scored on average 0.37 points lower on CR and 1.75 points higher on ldCT compared with reader 1. The SDCs were 3.8 and 14.6 for CR and ldCT, respectively.

Table 2 presents the patients showing a change (positive, negative or net) according to various cut-offs (ie, 0, 0.5 and SDC) for mSASSS and CTSS. Comparing any net change, a much higher percentage of patients showed positive change on ldCT versus CR (84% vs 46%, respectively). These numbers were similar for a cut-off of 0.5. However, using the SDC as cut-off, this difference disappeared (27% vs 32%, respectively). Figure 2 presents a double cumulative probability plot of the progression of

Table 2 Number of patients showing progression on CR or CT

Number of patients with progression according to mSASSS and CTSS* (n=37)		
	CR, n (%)	CT, n (%)
Change >0.0		
Positive	24 (65)	33 (89)
Negative	7 (20)	2 (5)
Net	17 (46)	31 (84)
Change >0.5		
Positive	22 (59)	33 (89)
Negative	6 (16)	2 (5)
Net	16 (43)	31 (84)
Change >SDC		
Positive	11 (30)	12 (32)
Negative	1 (3)	0 (0)
Net	10 (27)	12 (32)

Number of patients with progression defined by newly formed or growth of syndesmophytes† (n=50)						
	Reader 1		Reader 2		Consensus‡	
New	CR, n (%)	CT, n (%)	CR, n (%)	CT, n (%)	CR, n (%)	CT, n (%)
≥1	27 (54)	43 (86)	30 (60)	44 (88)	19 (38)	21 (42)
≥2	14 (28)	38 (76)	14 (28)	41 (82)	7 (14)	15 (30)
≥3	6 (12)	32 (64)	8 (16)	30 (60)	2 (4)	10 (20)
Growth						
≥1	10 (20)	35 (70)	7 (14)	32 (64)	3 (6)	16 (32)
≥2	8 (16)	36 (52)	6 (12)	27 (54)	3 (6)	11 (22)
≥3	2 (4)	23 (46)	4 (8)	18 (36)	1 (2)	6 (12)
New or growth						
≥1	28 (56)	45 (90)	33 (66)	48 (96)	21 (42)	25 (50)
≥2	18 (36)	42 (82)	19 (38)	44 (88)	9 (18)	20 (40)
≥3	12 (24)	36 (72)	12 (24)	38 (76)	3 (6)	15 (30)

*In the comparison of progression according to the mSASSS and CTSS, any progression is defined as progression above 0. SDC for CR was 3.8, and for CT 14.6.
†In the comparison of progression according to syndesmophytes, a comparison of the number of patients with ≥1, ≥2 and ≥3 newly formed syndesmophytes and syndesmophytes that grew, as well as for the combination of new formation or growth, is given.
‡Both readers agree about the formation or growth of a syndesmophyte at the same vertebral corner/quadrant.
CR, conventional radiography; CTSS, CT Syndesmophyte Score; mSASSS, modified Stoke AS Spine Score; SDC, smallest detectable change.

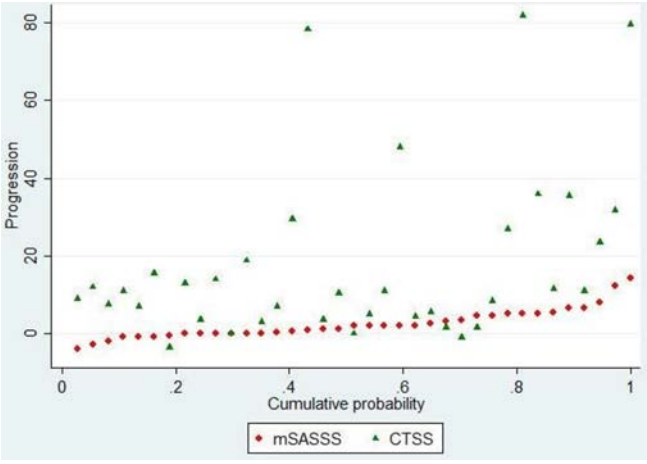


Figure 2 Cumulative probability plot of the progression of individual patients for mSASSS and CTSS (n=37). Average progression scores of the two readers for mSASSS and CTSS, ordered by mSASSS, are presented in a vertical line per patient. CTSS, CT Syndesmophyte Score; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score.

mSASSS and CTSS scores of individual patients. For 33 out of 37 patients, progression scores were higher for CTSS compared with mSASSS, although the scales of the two scoring methods are different.

Comparison of syndesmophytes on CR and ldCT

By comparing the number of patients with new and growing syndesmophytes on CR and ldCT for separate readers, it was clear that ldCT detected more patients with progression for both new formation and growth of syndesmophytes and for all cut-off levels (table 2). Also, with the strict consensus definition, this difference between CR and ldCT was present. It was especially apparent in case of growth and for cut-offs of a higher number of syndesmophytes per patient. For individual readers, three times as many patients showed any bony proliferation at ≥3 quadrants on ldCT compared with corners on CR. With the consensus definition, five times as many patients showed any bony proliferation at ≥3 quadrants on ldCT compared with corners on CR.

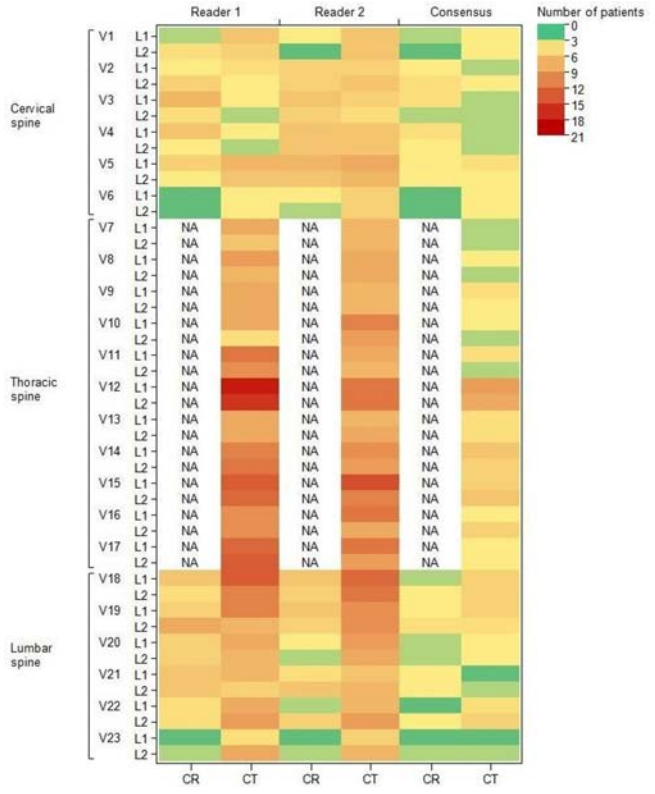


Figure 3 Heatmap of the number of patients with a new syndesmophyte or growth of a syndesmophyte per corner/quadrant from the Sensitive Imaging in Ankylosing Spondylitis cohort (n=50) for individual readers and consensus. CR, conventional radiograph; L, level; NA, not applicable; VU, vertebral unit.

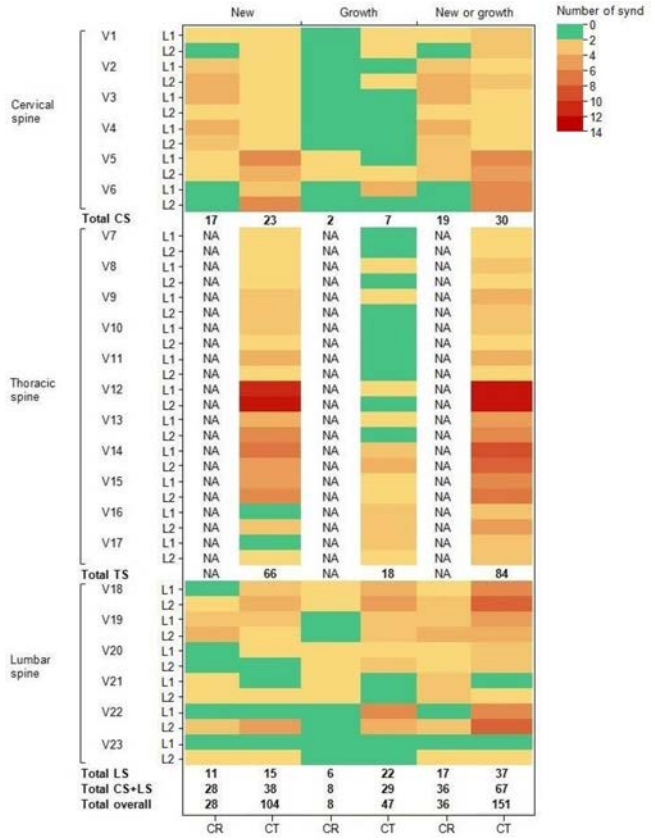


Figure 4 Heatmap of the number of new syndesmophytes, growing syndesmophytes, or the combination of new or growing syndesmophytes per corner/quadrant for 50 patients from the Sensitive Imaging in Ankylosing Spondylitis cohort for the consensus definition. CR, conventional radiograph; CS, cervical spine; L, level; LS, lumbar spine; NA, not applicable; synd, syndesmophytes; TS, thoracic spine; VU, vertebral unit.

When comparing the number of patients with new or growing syndesmophytes per level, it was apparent that the largest number of patients showed this bony proliferation in the thoracic spine (figure 3; for actual values per level, see online supplementary table 3). This was evident for both the individual readers and for the consensus score. For the lumbar spine and the upper and lower sections of the cervical spine, more patients showed bony proliferation on ldCT than on CR when comparing scores for individual readers. This advantage of the ldCT was not present for the middle section of the cervical spine. When comparing the cervical and lumbar spine using the consensus score, the difference between CR and ldCT was still present, but much less obvious. As analysing the number of patients with bony proliferation is an insensitive method to detect differences between CR and ldCT, we subsequently analysed the number of new or growing syndesmophytes per level. We present this only for the consensus score.

When comparing the number of new or growing syndesmophytes per level on ldCT and CR, more syndesmophytes were seen on ldCT on almost all levels (figure 4; for actual values per level, see online supplementary table 4). Consistent with the analysis on patient level, most syndesmophytes were seen in the thoracic spine. When combining the cervical and lumbar spine, 28 new syndesmophytes were seen on CR compared with 38 on ldCT. The difference was much larger for growing syndesmophytes, with 8 on CR compared with 29 on ldCT. When comparing all available levels on CR (cervical and lumbar) with ldCT (cervical, thoracic and lumbar), the difference was even larger, with 28 new syndesmophytes seen on CR as opposed to 104 on ldCT and 8 growing syndesmophytes on CR compared with 47 on ldCT. When looking at any bony proliferation, 36 new or growing syndesmophytes were seen on CR compared with 151 on ldCT.

DISCUSSION

The present study, performed in a cohort of patients with AS, found that more bone proliferation was detected on ldCT compared with CR. Most progression was detected in the thoracic spine. ldCT detected nearly five times more new or growing syndesmophytes compared with CR. The difference between CR and ldCT was most striking for the detection of growing syndesmophytes. Furthermore, even with the strict consensus definition, five times more patients showed any bone proliferation at ≥3 quadrants on ldCT compared with corners on CR, and almost five times as many new or growing syndesmophytes were seen.

Compared with CR, ldCT has multiple advantages. The most important difference is the volume data acquisition with the possibility of multislice multiplanar reconstruction. This increases the sensitivity to detect bone formation. Lateral CRs only show an overprojection of the medial and lateral part of a vertebra, and the posterior corners on the lateral view of the CR cannot be assessed reliably.[13] The thoracic spine is even not included in the scoring system of the CR, since overprojection of soft and bony tissues but also scoliosis or kyphosis limit correct interpretation or measurement of syndesmophytes. On ldCT, syndesmophytes

can be analysed in any plane, correcting for spinal curvatures. Moreover, in a previous study of the spatial distribution of syndesmophytes along the vertebral rim in patients with AS, it was found that most syndesmophytes are present on the posterolateral rim.[14] On ldCT both endplates of a vertebra are divided in four quadrants in which syndesmophytes can be analysed compared with only one anterior corner on CR. Another advantage is the high spatial resolution, showing more detailed bony anatomy and the possibility to detect smaller syndesmophytes. This could enable earlier identification of progression; however, it could also introduce measurement error. The fact that there is a major reduction in the percentage of patients showing any progression of bony proliferation if we switch from the individual reader (at least 90%) to the consensus score (50%) could be interpreted as modest reliability. However, it should be realised that the agreement is at the level of the quadrant. Moreover, ldCT is superior to CR with regard to the number of patients excluded from analyses due to too many missing VCs or quadrants. This is mostly due to the fact that ldCT does not have the problem of overprojection, while on lateral CR of the cervical spine the lowest VCs are often missing because shoulders are raised due to a fixed kyphosis. All these advantages will likely help in enhancing the feasibility of trials in AS. Finally, the sacroiliac joints can also be assessed on CT, thereby eliminating the need for CR of these joints.

This study is unique in that, to our knowledge, it is the first study to directly compare the assessment of bone proliferation on CR and ldCT in a cohort of patients with AS. One of the strengths of this study is that both CR and ldCT were assessed by the same readers, although in separate reading sessions. Another important strength is that the strictest consensus definition was used. Even with this definition, the advantage of ldCT over CR for the identification of new or growing syndesmophytes is obvious.

The disadvantage of ldCT is the radiation dose, which is in general 10 times lower than the dose of a regular CT but 10 times higher than the dose of CRs. Using a phantom study this was confirmed for the SIAS study.[7 15] The dose for ldCT of the whole spine is approximately 4 mSv. With further technical advances, it may be expected that additional reduction in dosing will become possible. The mean radiation dose in a study by Diekhoff *et al*[16] on ldCT of the sacroiliac joints was 0.51 (SD 0.18) mSv. In general, the use of ldCT is in line with the guidelines from the European Commission.[17 18] However, we would like to stress that the use of ldCT is intended for clinical research and not daily clinical practice. Other possible disadvantages are the accessibility and costs.

Most gain in sensitivity is in the thoracic spine when both the formation of new syndesmophytes and growth of existing syndesmophytes are taken into account. If the aim is to reduce radiation exposure, it could be an option to image the thoracic spine only. However, it should be kept in mind that this could easily lead to a method with ceiling problems as >30% of the patients had already the maximum score in 9 of the 12 thoracic VUs.[7]

Another point of discussion is that the SDC of the mSASSS in our study is rather large (3.8) compared with earlier studies (between 2 and 2.9).[10 19 20] This difference can partly be explained by the fact that in our study readers were blinded to time point, while in two of these studies chronology was known, which is known to reduce reader variability.[5] Furthermore, in the current study, the mSASSS progression was higher than in the other cohorts.[21] However, by using consensus scores when comparing the detection of new and/or growth of syndesmophytes between imaging techniques, we took variation in reading into account.

In summary, we compared scoring methods for the analysis of bone proliferation on ldCT and CR and found that ldCT detects more bone proliferation in patients with AS. The biggest advantages of ldCT were the ability to analyse the thoracic spine and the opportunity to analyse growth of syndesmophytes in more detail. With this scoring method, it has now become feasible to use ldCTs, with a relatively low radiation dose, in research (eg, medication trials). Next steps will be to evaluate discrimination between treatments and test if a shorter interval for ldCT can pick up sufficient change.

Contributors DvdH designed the study. AdK, FdB, RvdB, SR performed the data analyses. XB, JB, FAvG, MR, RvdB performed the data collection. AdK, FdB prepared the first draft of the manuscript. All authors interpreted the results, commented on the draft manuscript and approved the final submission.

Funding The authors would like to thank the Dutch Rheumatism Association for providing a grant for the SIAS study. Reumafonds, 9-1-301.

Competing interests None declared.

Ethics approval Medical Ethics Committee in Leiden and in Herne.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Machado P, Landewé R, Braun J, *et al*. Both structural damage and inflammation of the spine contribute to impairment of spinal mobility in patients with ankylosing spondylitis. *Ann Rheum Dis* 2010;69:1465–70.
2 Wanders A, Landewé R, Dougados M, *et al*. Association between radiographic damage of the spine and spinal mobility for individual patients with ankylosing spondylitis: can assessment of spinal mobility be a proxy for radiographic evaluation? *Ann Rheum Dis* 2005;64:988–94.
3 Landewé R, Dougados M, Mielants H, *et al*. Physical function in ankylosing spondylitis is independently determined by both disease activity and radiographic damage of the spine. *Ann Rheum Dis* 2009;68:863–7.
4 Creemers MC, Franssen MJ, van't Hof MA, *et al*. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. *Ann Rheum Dis* 2005;64:127–9.
5 Wanders A, Landewé R, Spoorenberg A, *et al*. Scoring of radiographic progression in randomised clinical trials in ankylosing spondylitis: a preference for paired reading order. *Ann Rheum Dis* 2004;63:1601–4.
6 Spoorenberg A, de Vlam K, van der Linden S, *et al*. Radiological scoring methods in ankylosing spondylitis. Reliability and change over 1 and 2 years. *J Rheumatol* 2004;31:125–32.
7 de Bruin F, de Koning A, van den Berg R, *et al*. *Development of the Computed Tomography Syndesmophyte Score (CTSS) in patients with Ankylosing Spondylitis: data from the SIAS cohort [submitted companion manuscript]*.
8 Braun J, Baraliakos X. Imaging of axial spondyloarthritis including ankylosing spondylitis. *Ann Rheum Dis* 2011;70(Suppl 1):i97–i103.
9 van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361–8.
10 Ramiro S, van Tubergen A, Stolwijk C, *et al*. Scoring radiographic progression in ankylosing spondylitis: should we use the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) or the Radiographic Ankylosing Spondylitis Spinal Score (RASSS)? *Arthritis Res Ther* 2013;15:R14.
11 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307–10.
12 Bruynesteyn K, Boers M, Kostense P, *et al*. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. *Ann Rheum Dis* 2005;64:179–82.
13 Wanders AJ, Landewé RB, Spoorenberg A, *et al*. What is the most appropriate radiologic scoring method for ankylosing spondylitis? A comparison of the available methods based on the outcome measures in rheumatology clinical trials filter. *Arthritis Rheum* 2004;50:2622–32.
14 Tan S, Dasgupta A, Yao J, *et al*. Spatial distribution of syndesmophytes along the vertebral rim in ankylosing spondylitis: preferential involvement of the posterolateral rim. *Ann Rheum Dis* 2016;75:1951–7.
15 Teeuwisse W, Geleijns J, Veldkamp W. An inter-hospital comparison of patient dose based on clinical indications. *Eur Radiol* 2007;17:1795–805.

16 Diekhoff T, Hermann KG, Greese J, *et al*. Comparison of MRI with radiography for detecting structural lesions of the sacroiliac joint using CT as standard of reference: results from the SIMACT study. *Ann Rheum Dis* 2017;76:1502–8.
17 Mettler FA, Huda W, Yoshizumi TT, *et al*. Effective doses in radiology and diagnostic nuclear medicine: a catalog. *Radiology* 2008;248:254–63.
18 Radiation protection 99. *Guidance on medical exposures in medical and biomedical research*. Brussels, Belgium: European Commission, 1998:p. 1–14. https://ec.europa.eu/energy/sites/ener/files/documents/099_en.pdf (accessed 27 June 2017).
19 Baraliakos X, Listing J, Rudwaleit M, *et al*. Progression of radiographic damage in patients with ankylosing spondylitis: defining the central role of syndesmophytes. *Ann Rheum Dis* 2007;66:910–5.
20 Maas F, Arends S, Brouwer E, *et al*. Reduction in spinal radiographic progression in ankylosing spondylitis patients receiving prolonged treatment with TNF-alpha inhibitors. *Arthritis Care Res* 2016.
21 Ramiro S, Stolwijk C, van Tubergen A, *et al*. Evolution of radiographic damage in ankylosing spondylitis: a 12 year prospective follow-up of the OASIS study. *Ann Rheum Dis* 2015;74:52–9.

OPEN ACCESS

EXTENDED REPORT

Monocyte alterations in rheumatoid arthritis are dominated by preterm release from bone marrow and prominent triggering in the joint

Biljana Smiljanovic,[1] Anna Radzikowska,[2] Ewa Kuca-Warnawin,[2] Weronika Kurowska,[2] Joachim R Grün,[3] Bruno Stuhlmüller,[1] Marc Bonin,[1] Ursula Schulte-Wrede,[3] Till Sörensen,[1] Chieko Kyogoku,[3] Anne Bruns,[1] Sandra Hermann,[1] Sarah Ohrndorf,[1] Karlfried Aupperle,[1] Marina Backhaus,[1] Gerd R Burmester,[1] Andreas Radbruch,[3] Andreas Grützkau,[3] Wlodzimierz Maslinski,[2] Thomas Häupl[1]

Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-211649).

[1]Department of Rheumatology and Clinical Immunology, Charité Universitätsmedizin, Berlin, Germany
[2]Department of Pathophysiology and Immunology, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, Poland
[3]Deutsches Rheuma Forschungszentrum Berlin (DRFZ), A Leibniz Institute, Berlin, Germany

Correspondence to
Dr. Thomas Häupl, Department of Rheumatology and Clinical Immunology, Charité Universitätsmedizin, Berlin, 10117, Germany; thomas.haeupl@charite.de

AR and EK-W contributed equally.

Received 13 April 2017
Revised 12 October 2017
Accepted 10 November 2017
Published Online First 30 November 2017

To cite: Smiljanovic B, Radzikowska A, Kuca-Warnawin E, *et al*. *Ann Rheum Dis* 2018;**77**:300–308.

ABSTRACT

Objective Rheumatoid arthritis (RA) accompanies infiltration and activation of monocytes in inflamed joints. We investigated dominant alterations of RA monocytes in bone marrow (BM), blood and inflamed joints.

Methods $CD14^+$ cells from BM and peripheral blood (PB) of patients with RA and osteoarthritis (OA) were profiled with GeneChip microarrays. Detailed functional analysis was performed with reference transcriptomes of BM precursors, monocyte blood subsets, monocyte activation and mobilisation. Cytometric profiling determined monocyte subsets of $CD14^{++}CD16^-$, $CD14^{++}CD16^+$ and $CD14^+CD16^+$ cells in BM, PB and synovial fluid (SF) and ELISAs quantified the release of activation markers into SF and serum.

Results Investigation of genes differentially expressed between RA and OA monocytes with reference transcriptomes revealed gene patterns of early myeloid precursors in RA-BM and late myeloid precursors along with reduced terminal differentiation to $CD14^+CD16^+$monocytes in RA-PB. Patterns associated with tumor necrosis factor/lipopolysaccharide (TNF/LPS) stimulation were weak and more pronounced in RA-PB than RA-BM. Cytometric phenotyping of cells in BM, blood and SF disclosed differences related to monocyte subsets and confirmed the reduced frequency of terminally differentiated $CD14^+CD16^+$monocytes in RA-PB. Monocyte activation in SF was characterised by the predominance of $CD14^{++}CD16^{++}CD163^+$HLA-$DR^+$ cells and elevated concentrations of sCD14, sCD163 and S100P.

Conclusion Patterns of less mature and less differentiated RA-BM and RA-PB monocytes suggest increased turnover with accelerated monocytopoiesis, BM egress and migration into inflamed joints. Predominant activation in the joint indicates the action of local and primary stimuli, which may also promote adaptive immune triggering through monocytes, potentially leading to new diagnostic and therapeutic strategies.

INTRODUCTION

The principal pathological changes in rheumatoid arthritis (RA) occur in the synovial joints, where inflammation leads to cartilage and bone destruction, thereby reducing physical abilities and quality of life.[1 2] Infiltration of monocytes along with T and B cells into the joint and production of inflammatory mediators characterise the immunopathology of this disease. The influence of the monocytic lineage in shaping the immune response is substantial and interferes with both the innate and adaptive arm of immunity. Thus, it is not surprising that controlling inflammation in disease-modifying antirheumatic drug (DMARD) non-responders may be achieved when targeting monocyte-derived cytokines, tumour necrosis factor (TNF), interleukin (IL)-1, IL-6 or monocyte T cell interaction.

Human monocytes represent 5%–10% of the blood leucocytes and their half-life in the vascular compartment is 1 - 3 days.[3–5] Based on CD14 and CD16 expression levels, monocytes are categorised into three subsets: classical $CD14^{++}CD16^-$, intermediate $CD14^{++}CD16^+$ and non-classical $CD14^+CD16^+$.[6] Developmental relationship between the subsets was demonstrated in mice, macaques and humans.[7–9] Classical monocytes are the dominant blood population expressing CCR2, a receptor involved in mobilisation from bone marrow (BM) and recruitment to inflammatory sites.[10 11] In contrast, non-classical monocytes reduce CCR2 but elevate CX3CR1 surface expression, which is needed for patrolling blood vessels and migrating into resting tissues.[6 12] Intermediate monocytes express CCR2 and CX3CR1 on intermediate level and show the highest HLA-DR expression.[13]

Monocytes develop characteristic gene expression profiles, in systemic lupus erythematosus (SLE) and RA, which are largely influenced by IFN and TNF, respectively.[14] It has been shown that even a single biomarker on monocytes might be sufficient to quantify disease activity, like SIGLEC-1 in SLE, or to predict responsiveness to anti-TNF biologicals, like CD11c in RA.[15 16] Furthermore, frequencies of classical, intermediate and non-classical blood monocytes were found to alter in patients with RA compared with healthy donors.[17–19] The frequencies of blood subsets were skewed by glucocorticoid treatment and may be predictive for the clinical response to methotrexate (MTX) or MTX plus anti-TNF treatment.[13 20–22] However, results are in part contradictory, which might be explained

by different techniques of monocyte purification and by difficulties to capture intermediate monocytes properly.[23] In general, it was assumed that in inflammatory conditions, such as RA, phenotypical and quantitative alterations affect monocyte blood subsets and are associated with release of immature and younger myeloid cells from BM.[24] This so called 'left-shift' in monocytopoiesis can be suppressed, at least partially, with administration of certain drugs like anti-GM-CSF and MTX.[25]

To investigate the role and involvement of monocytes in RA pathogenesis from a systemic point of view, we profiled transcriptomes of BM and blood monocytes. This comprehensive approach revealed left-shift patterns as dominant changes in both RA-BM and RA-peripheral blood (PB), suggesting increased turnover of RA monocytes, characterised with increased monocytopoiesis, faster egress from BM and skewed distribution of monocyte subsets. We therefore hypothesised that increased monocyte turnover might be associated with their recruitment into inflamed joints. To confirm these observations, we applied cytometric profiling of BM, PB and synovial fluid (SF) monocytes, which provided additional insight into heterogeneity and various differentiation stages of monocyte subsets in BM, blood and SF.

MATERIALS AND METHODS

Sample collection for transcriptome, flow cytometry and ELISA analyses

All samples for transcriptome analysis and paired samples of BM and blood for cytometry were collected at the Rheumoorthopaedic Clinic of the Institute of Rheumatology in Warsaw, Poland. Paired samples of blood and SF investigated by cytometry and ELISA and blood samples from RA and healthy donors investigated by cytometry were collected at the Department of Rheumatology of the Charité Universitätsmedizin, Berlin, Germany. All patients gave written informed consent. Patients' characteristics are summarised in table 1. Detailed overview of sample collection and processing is included in online supplementary material.

RNA isolation, Affymetrix GeneChip hybridisation and quality controls for gene expression analyses

RNA preparation, quality controls and array hybridisation were performed as previously described and were included in online supplementary material.[26 27]

Statistical and functional analyses of microarray data

Analysis with the BioRetis database (www.bioretis.com) consisted of MAS5.0 pair-wise comparison statistics as previously described to select probe sets differentially expressed in at least 60% of all pair-wise comparisons between RA and osteoarthritis (OA) samples.[14 27–29] Details of functional interpretation with Gene Ontology (GO), Ingenuity Pathway Analysis (IPA) and comparison with reference signatures are provided in online supplementary material.

Analysis of flow cytometry data

Matched BM and blood samples from patients with OA and RA, matched blood and synovial samples from patients with RA and blood samples from RA and healthy donors were analysed by unsupervised clustering with *immuno*Clust.[30]

Statistical analyses of protein data

GraphPad Prism V.6.0b was used for statistical analysis of ELISA data. Groups were compared by Mann-Whitney U-test, and

Table 1 Clinical data of patients included in the study

	Bone marrow samples for transcriptome analysis		Blood samples for transcriptome analysis		Bone marrow samples for flow cytometry analysis		Blood samples for flow cytometry analysis		Synovial fluid and blood samples used for cytometric analysis	Blood samples for flow cytometry analysis (validation cohort)		Synovial fluid and serum samples used for ELISA	
	RA patients	QA patients	RA patients	QA patients	RA patients	QA patients	RA patients	QA patients	RA patients	RA patients	ND (healthy donors)	RA patients	QA patients
No. of patients	8	8	6	6	11	9	11	9	6	12	12	17	16
Gender, no. female/no. male	8/0	4/4	5/1	2/4	10/1	7/2	10/1	7/2	*610*	10/2	10/2	14/3	10/6
Age, years	55 (48.5–58.5)	55 (53.75–58.5)	56 (54.5–58.25)	54.5 (52.5–61)	59 (55.5–60.5)	59 (52–64)	59 (55.5–60.5)	59 (52–64)	31.5 (23.5–58.25)	49 (40.75–53)	36.6 (31.05–43.50)	59 (51–69)	61.5 (54–67.5)
RF positive, (%)									66.7	66.7		73.3	
ACPA positive, (%)									50	75		57	
TJC28									1 (1–1)	5.5 (3–9)		9 (3–12)	2 (1–2.25)
SJC28									1 (1–1)	3 (1.75–6)		2 (1–5)	1 (1–2)
VAS disease activity (0–10 cm)									5 (4.25–6.25)	5 (3.75–7)		6 (4–6.25)	5 (4–6)
ESR (mm/L h)	26 (10.25–34)	6 (3–15)	27 (24.5–46.75)	9.5 (4.25–13.25)	18 (12.5–34)	12 (11–21)	18 (12.5–34)	12 (11–21)	29 (23.25–34.75)	24.5 (17–26.5)	6 (5.5–6)	43 (25.75–64)	18 (9–23)
CRP (mg/dL)										6.35 (3.5–9.8)		1.52 (0.60–3.68)	0.52 (0.47–0.70)
DAS28-ESR									3.82 (3.67–3.85)	4.51 (4.15–5.52)		5.48 (3.80–6.08)	3.74 (3.29–4.13)

Values provide the median with IQR.
ACPA, anticyclic citrullinated peptide antibodies; CRP, C reactive protein; DAS28, DiseaseActivity Score in 28 joints; ESR, erythrocyte sedimentation rate; ND, healthy donor; OA, osteoarthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC28, 28 joint swollen joint count; TJC28, 28 joint tender joint count; VAS, visual analogue scale.

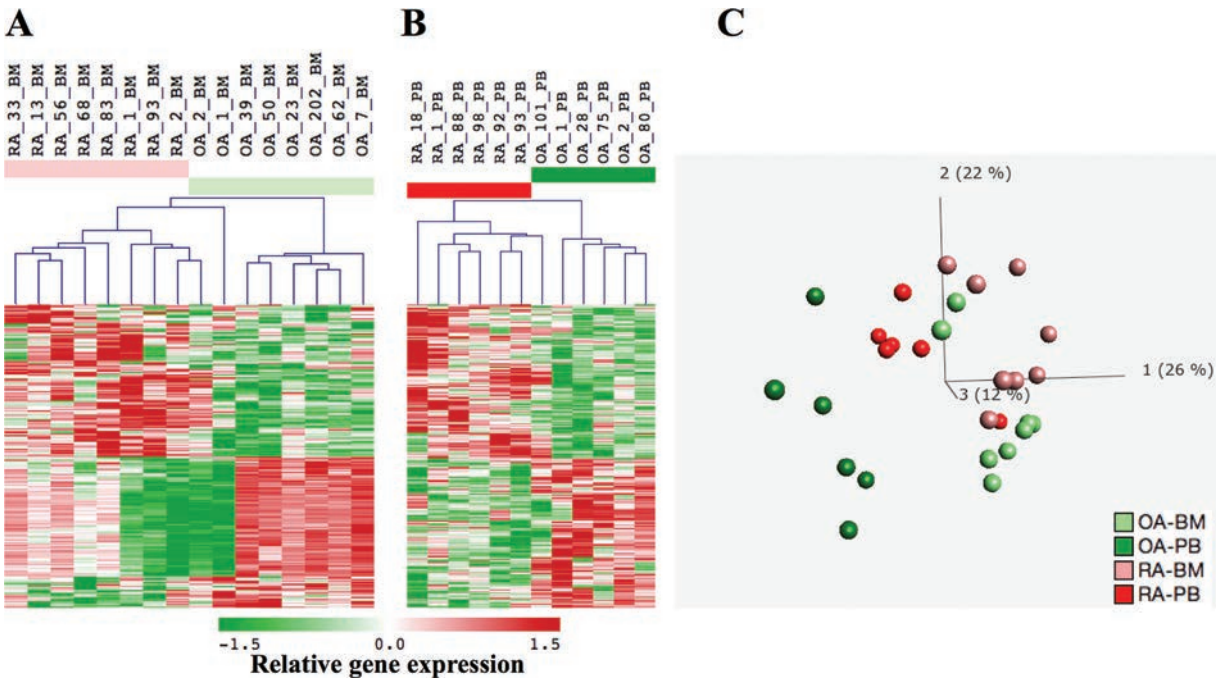


Figure 1 Genes differentially expressed between RA and OA in BM and blood monocytes. Hierarchical clustering was performed with (A) eight RA-BM and eight OA-BM profiles defined by 221 probe sets (141 genes) and with (B) six RA-PB and six OA-PB profiles defined by 379 probe sets (286 genes; Affymetrix annotation release 35; 4/16/15). Rows represent the probe sets, and columns represent the samples with relative intensities as indicated by the scale bar. (C) Using the combined set of 571 probe sets differentially expressed in BM and blood profiles, principal components analysis (PCA) revealed the largest distance between OA-PB and RA-BM monocytes, while RA-PB monocytes shifted towards BM. The first three principal components, PC1, PC2 and PC3, explained 26%, 22% and 12% of the variance in the data set, respectively. BM samples were coloured in light red (RA) and light green (OA) and blood samples in red (RA) and green (OA). BM, bone marrow; OA, osteoarthritis; PB, peripheral blood; RA, rheumatoid arthritis.

P values <0.05 were considered significant. For comparing monocyte subsets between groups, either unpaired or paired t-test was applied (described in figure legends).

RESULTS

RA-related transcriptional changes in BM, and blood monocytes are different and more prominent in blood

Comparison between BM monocytes from patients with RA and OA identified differential expression of 221 probe sets. Probe sets upregulated in RA (n=111) performed better to distinguish between RA and OA (figure 1A and online supplementary table 1). Comparison between blood monocytes from RA and OA revealed 379 differentially expressed probe sets (figure 1B and online supplementary table 2). Leading genes upregulated in RA-BM included *TMTC1*, *HOPX*, *IL1R2*, *FLT3* and *CLU*, while those upregulated in RA-PB monocytes included *CCR2*, *CXCR4*, *CD163*, *IL1R2* and *S100P*. Altogether, BM and PB revealed 571 differentially expressed probe sets with only 29 common for both compartments (online supplementary table 3). Principal component analysis (PCA) with all differentially expressed probe sets from BM and PB showed that RA-PB were localised between OA-PB and samples from BM (figure 1C and online supplementary movie). Calculated distances between RA-PB, OA-PB, RA-BM and OA-BM confirmed proximity of RA-PB samples to RA-BM and OA-BM (online supplementary figure 1).

GO and IPA suggest altered haemopoiesis, antiapoptosis and inflammatory response in RA

GO and IPA annotated the differences in RA-BM and RA-PB monocytes to 'inflammatory response', 'anti-apoptosis' and 'hemopoiesis' (online supplementary table 4). The dominant molecular network was characterised by interleukin (*IL*)-*8* and *IL10* in RA-BM and by *TNF* and *CCL2* in RA-PB monocytes (online supplementary figure 2). Although with only few genes overlapping, all three functions were evident both in RA-BM and RA-PB monocytes.

Reference transcriptomes disclosed functional patterns of precursor activity and weak inflammatory response in RA BM and blood

This more comprehensive functional analysis for development, differentiation and activation of monocytes was guided by (1) the proximity of RA-PB monocytes to BM samples as shown by PCA and (2) altered haemopoiesis and inflammation as suggested by GO and IPA, since these alterations were common both for RA-BM and RA-PB monocytes. For this purpose, we selected transcriptomes from Gene Expression Omnibus, which provide a reference for the myeloid lineage of haemopoiesis in BM, monocyte activation and differentiation in blood and cell mobilisation from BM into blood triggered by G-CSF.[8 14 27 31 32] In these reference transcriptomes, we tested differentially expressed genes in RA and OA monocytes for their involvement in myelopoiesis, monocyte differentiation, activation and mobilisation.

Analysis of RA-BM upregulated genes emphasised few clusters: early and late myelopoiesis, G-CSF mobilisation and TNF/LPS stimulation (figure 2A–C). The early myelopoietic cluster included genes highly expressed in haematopoietic stem cells (HSC) and early BM progenitors. The late myelopoietic cluster depicted genes highly expressed in band cells (BC) and polymorphonuclear (PMN) from BM and partially overlapped with the G-CSF cluster. Discontinuation of the early haematopoietic cluster and onset of the late myelopoietic cluster in RA-BM monocytes occurred at the stage of

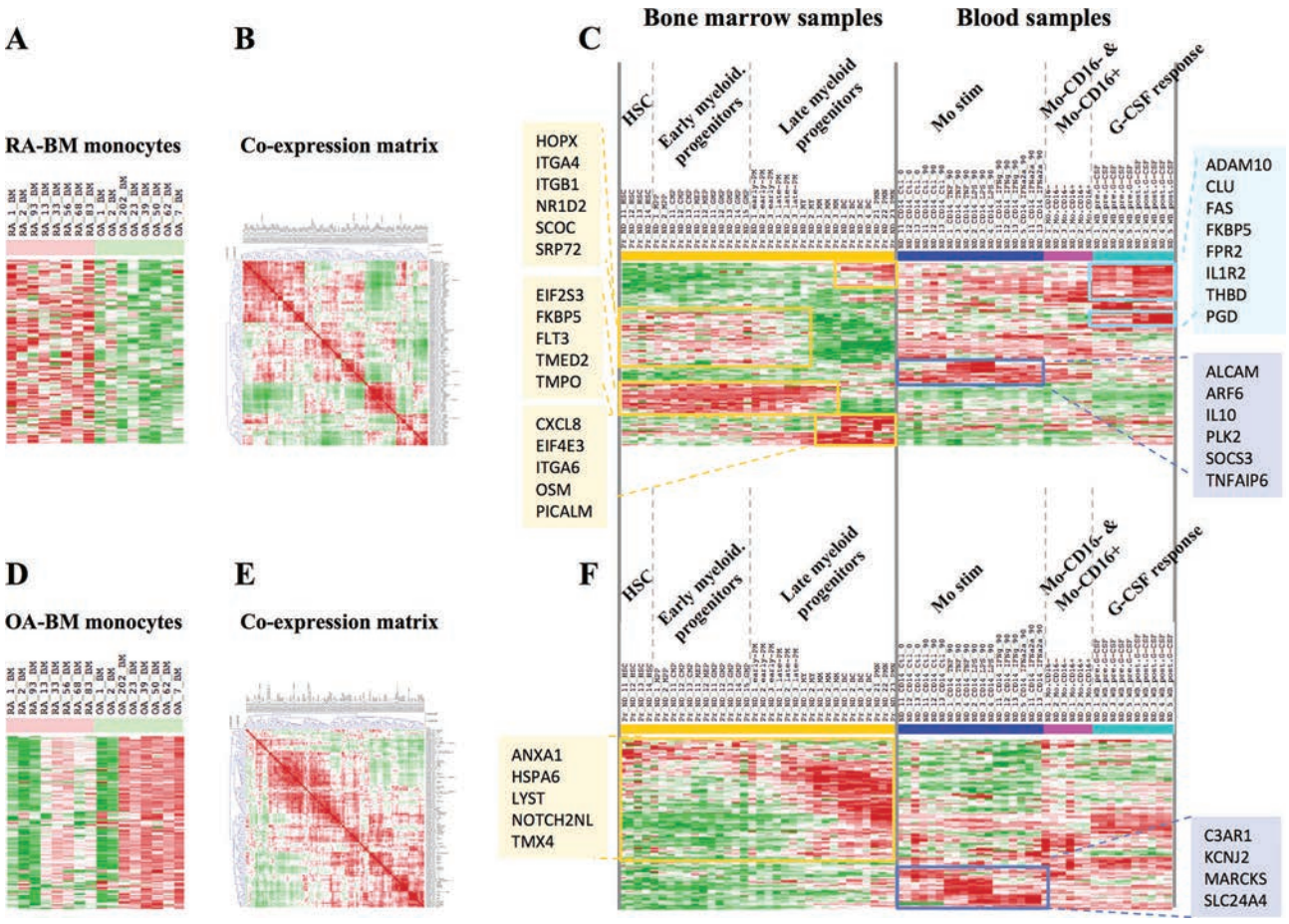


Figure 2 Identification of the functional patterns in RA and OA BM monocytes based on reference transcriptomes. Reference transcriptomes for myelopoiesis (n=34), monocyte activation (n=18), differentiation (n=8) and G-CSF induced leucocyte mobilisation (n=8) were applied to recognise functional patterns in the 221 probe sets differentially expressed between RA-BM and OA-BM monocytes. In total, 111 probe sets were upregulated in RA (A–C) and 110 were upregulated in OA (D–F). The signal intensities from the reference transcriptomes (C and F) were correlated, and obtained correlation coefficients were hierarchically clustered as shown by matrices in B and E. The orders of probe sets determined by these matrices were applied to sort 111 probe sets in RA (A) and 110 probe sets in OA (D). The same orders were applied to sort probe sets of the 68 reference transcriptomes in C and F. Calculation of scores that demonstrated relevance of identified functional patterns is included in online supplementary figures 9–13. Red indicates increased signal expression (max=2) or positive correlation (max=1), and green indicates decreased signal expression (min=−2) or negative correlation (min=−1). Samples in A and D represented RA-BM (n=8, light red) and OA-BM (n=8, light green). Samples in C and F, coloured in yellow, included haematopoietic stem cells (HSC; n=4), multipotent progenitors (MPP; n=2), common myeloid progenitors (CMP; n=3), megakaryocyte–erythrocyte progenitors (MEP; n=2), granulocyte–monocyte progenitors (GMP, n=5), early promyelocytes (early-PM; n=3), late promyelocytes (late-PB; n=3), myelocytes (MY; n=2), metamyelocytes (MM; n=3), band cells (BC; n=4) and polymorphonuclear cells (PMN; n=3). Samples in C and F, coloured blue, included blood monocytes: unstimulated for 0 min (Ctr_0, n=3), unstimulated for 90 min (Ctr_90, n=3,), stimulated for 90 min with TNF (n=3), or LPS (n=3) or IFNγ (n=3) or IFNα (n=3). Samples in C and D, coloured in violet, included monocyte subsets of Mo-CD16– (n=3) and Mo-CD16+ (n=3). Samples in C and D, coloured in cyan, included all leucocytes before G-CSF stimulation (WB pre.G-CSF, n=5) and after stimulation with G-CSF for 5 days (WB post.GCSF, n=5). BM, bone marrow; G-CSF, granulocyte-colony stimulating factor; IFNα, interferon alpha; IFNγ, interferon gamma; LPS, lipopolysaccharide; OA, osteoarthritis; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

myelocytes/metamyelocytes (MY/MM). This observation complements the line of evidence reported for granulocytopoiesis in BM, which shows that the MY/MM developmental stage is crucial for termination of proliferation and subsequent acquisition of phagocytic potential.[33] Thus, applying transcriptomes of early myeloid and late myeloid progenitors committed to the granulocyte lineage, we identified (1) a cluster common for BM monocytes and early progenitors and (2) a cluster common for monocytes and granulocytes. Furthermore, the G-CSF gene pattern was pronounced and consisted of genes expressed in purified monocytes like *ADAM10*, *CLU*, *FAS*, *IL1R2* and *THBD*. The cluster related to TNF/LPS response included *ALCAM1*, *ARF6*, *IL10*, *TNFAIP6* and *SOCS3*.

By analysing genes upregulated in OA-BM monocytes, we identified a cluster that dominated in late stage of myelopoiesis (figure 2D–F). Contrary to RA, no G-CSF-inducible pattern was evident in OA-BM monocytes.

Genes upregulated in RA-PB monocytes consisted of a late myelopoietic cluster, which was covered by the far more extensive cluster of genes inducible by G-CSF (figure 3A–C). It emphasised a left-shifted monocytopoiesis and faster mobilisation of monocytes from BM. The cluster related to TNF/LPS stimulation was more pronounced than in BM and included the genes *ADM*, *AQP9*, *S100P* and *TNFAIP6*. The cluster of terminally differentiated $CD14^{+}CD16^{+}$ monocytes was under-represented and indicated the reduced frequencies of this monocyte subset in RA-PB.

Analysis of upregulated genes in OA-PB disclosed a strong CD16+ cluster, depicted by the genes *CDKN1C*, *TCF7L2*, *CSF1R* and *MTSS1*. Similar to OA-BM monocytes, OA-PB

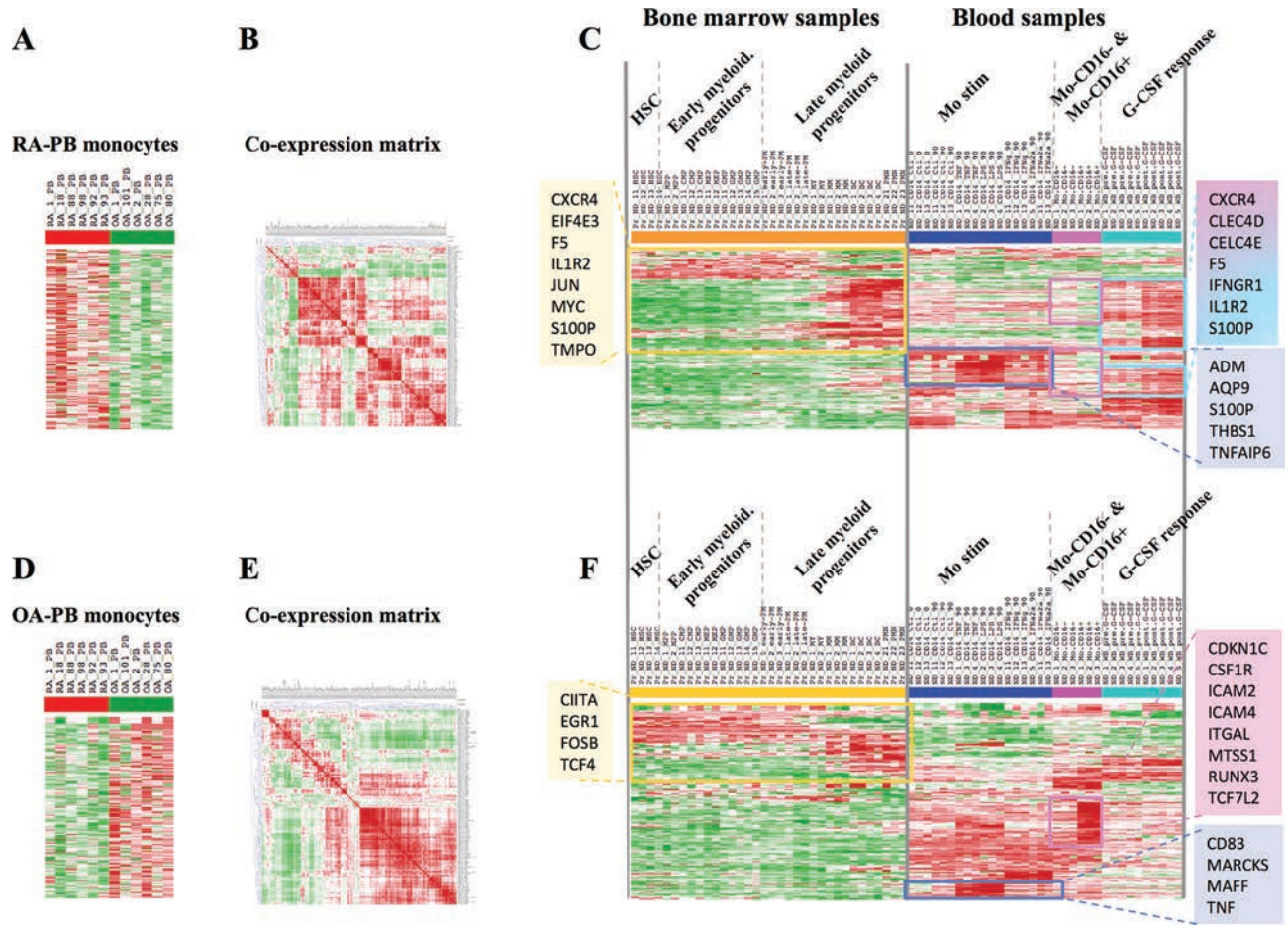


Figure 3 Identification of the functional patterns in RA and OA blood monocytes based on reference transcriptomes. In total, 379 probe sets were differentially expressed between RA-PB and OA-PB monocytes. They were divided into two groups: 192 probe sets upregulated in RA-PB (A–C) and 187 probe sets upregulated in OA-PB (D–F). They were analysed by the reference transcriptomes as described in figure 2. Samples were labelled as described in figure 2. Calculation of scores that demonstrated relevance of identified functional patterns is described in online supplementary material and included in online supplementary figures 9–13. G-CSF, granulocyte-colony stimulating factor; HSC, haematopoietic stem cells; OA, osteoarthritis; PB, peripheral blood; RA, rheumatoid arthritis.

monocytes did not exhibit a G-CSF pattern, indicating undisturbed kinetics of monocyte egress from BM (figure 3D–F).

Potential contamination of the blood monocytes from RA and OA patients with neutrophils, CD4+T−, CD8+T−, CD19+B- and CD56NK-cells was excluded by mapping the differentially expressed genes in RA and OA to cell type-specific transcriptomes in the coexpression analysis (online supplementary figure 3).

Cytometric profiling of BM, blood and SF confirmed transcriptome data and indicated monocyte activation in the joint

Automated analysis with the *immuno*Clust algorithm, unsupervised clustering tool, identified in the blood the three subsets of monocytes based on size, granularity, CD14, CD16 and HLA-DR expression (figure 4B).[30] Automated analysis of monocytes included (1) exclusion of dead cells and cell doublets and (2) exclusion of granulocytes and lymphocytes (online supplementary figures 4A,B and 5). All three compartments, BM, blood and SF, revealed their own distribution of monocyte subpopulations (figures 4 and 5). Classical monocytes were the dominant subset in BM and blood but were absent in SF. Intermediate monocytes were a minor subset in BM, increased in blood and were the dominant population in SF. Non-classical monocytes were absent in BM and clearly distinguishable in blood but less obvious in SF. Besides differences in CD14 and CD16 expression on these subpopulations, HLA-DR was highest in intermediate followed by non-classical and classical monocytes (figure 4F). CD163 also increased in intermediate but dropped in non-classical to the lowest level (figure 4G). Comparing RA with OA, BM subpopulations were similar in frequency but revealed decreased CD16 expression in RA (figure 4E). In blood, frequency of non-classical and expression of CD14 and HLA-DR on classical monocytes was reduced in RA (figure 4C–F).

In the synovial compartment, characteristics of subpopulations changed. The dominant intermediate population revealed higher CD14 and HLA-DR expression than in the blood and expressed high levels of CD16 (figure 5D–F). Percentage of $CD14^{++}CD16^{+}$ cells in SF correlated with inflammation (online supplementary figure 6A). Another population of $CD14^{+}CD16^{+}$ cells in SF did not exceed 20% of all monocytes and when compared with blood subsets, HLA-DR was similar to intermediate, CD14 reduced to levels of non-classical, CD16 was slightly higher than classical and CD163 was similar to classical and intermediate subsets. Their frequency was negatively correlated with erythrocyte sedimentation rate (online supplementary figure 6B). We validated the observed differences in frequency of monocyte subpopulations with independent blood samples and confirmed

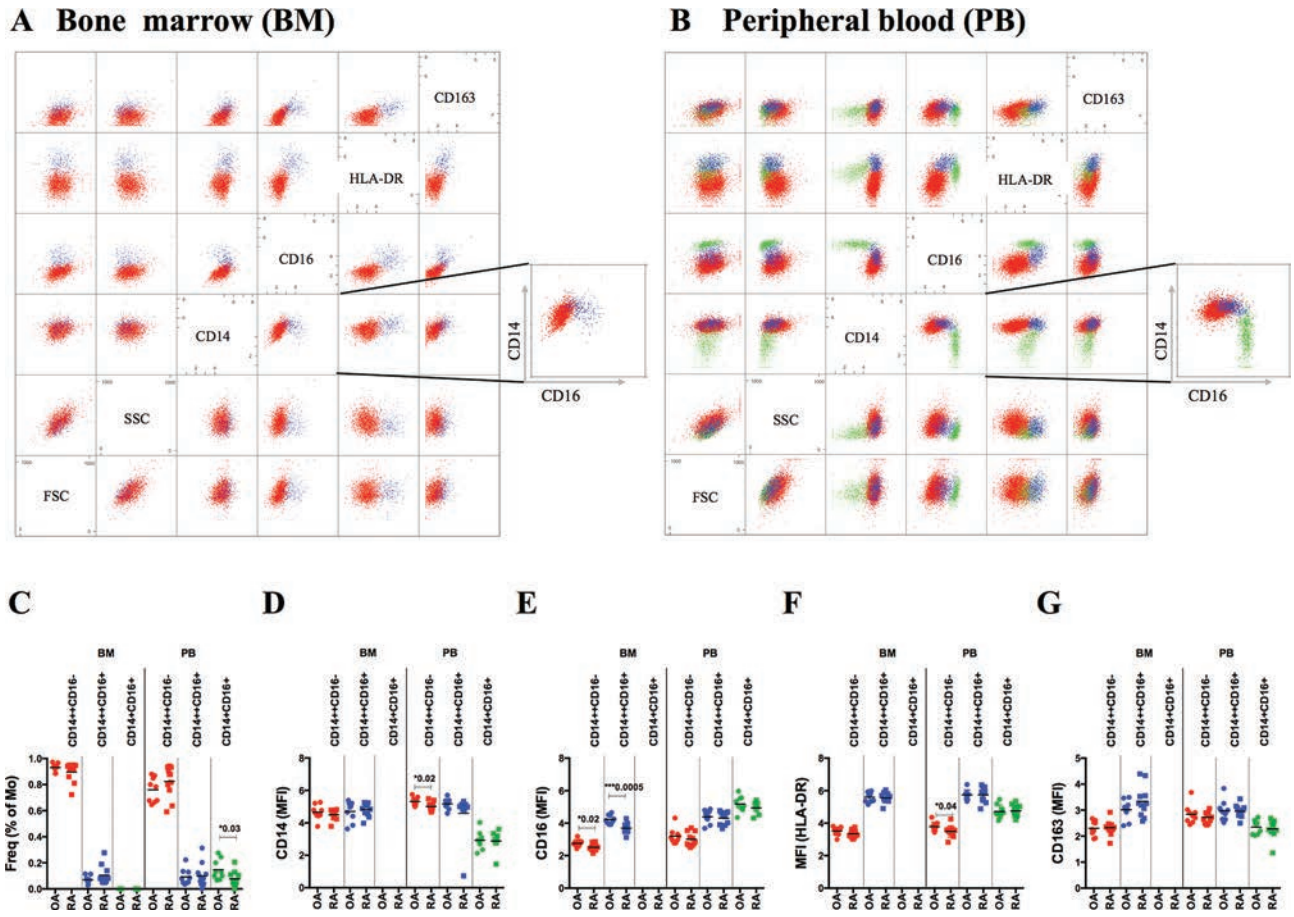


Figure 4 Cytometric analysis of monocyte subsets in BM and blood from patients with RA and OA. Paired BM and blood samples from OA (n=9) and RA (n=11) patients were investigated for CD14, CD16, CD163 and HLA-DR expression. Data were analysed by immunoClust. Scatterplot matrices from BM (A) and blood (B) samples of one representative patient demonstrate classical (CD14++CD16−; red), intermediate (CD14++CD16+; blue) and non-classical (CD14+CD16+; green) monocytes. Intermediate monocytes are distinguished from classical and non-classical by increased HLA-DR expression. (C) In BM, two monocyte subsets were detected (mean frequency of CD14+ cells±SD): CD14++CD16− (RA: 89.6%±7.2%; OA: 93.0%±3.0%) and CD14++CD16+ (RA: 10.4%±7.2%; OA: 7.0%±3.0%), while CD14+CD16+ monocytes were absent. In blood, three monocyte subsets were detected: CD14++CD16− (RA: 82.5%±12.0%; OA: 76.1%±9.5%), CD14++CD16+ (RA: 9.9%±9.1%; OA: 9.2%±6.1%) and CD14+CD16+ (RA: 7.6%±5.7%; OA: 14.7%±7.7%). Distribution of asinh-transformed median fluorescence intensity (MFI) is presented for CD14 (D), CD16 (E), HLA-DR (F) and CD163 (G). Differences in frequencies and in MFIs of CD14, CD16, HLA-DR and CD163 between RA and OA monocyte subsets in BM and blood were calculated by unpaired t-test and significance was indicated with P value. OA, osteoarthritis; RA, rheumatoid arthritis.

that non-classical monocytes are decreased in blood from RA patients when compared with healthy donors (online supplementary figure 7).

Markers shedded or released from monocytes confirm monocyte activation

The soluble markers sCD14, sCD163 and S100P, which relate to monocyte activation, were determined by ELISA in paired samples of serum and SF from RA and OA patients and in serum from healthy donors (online supplementary figure 8). Differences were highly significant between RA and OA in SF, and levels of sCD14 and S100P were up to 10 times higher in RA SF compared with serum. In serum, sCD14 and S100P were still able to discriminate RA both from OA and ND, while sCD163 discriminated RA only from ND.

DISCUSSION

This study identified that RA-related transcriptional changes in the monocyte lineage are dominated by left-shift patterns in BM and blood, suggesting increased monocytopoiesis, premature egress from BM and reduced differentiation in the blood. In detail, RA-BM profiles revealed patterns of (1) early myeloid precursor cells and (2) stimulated myelopoiesis (G-CSF), while RA-PB profiles depicted patterns of (1) late myelopoietic precursors, (2) extended G-CSF induction and (3) reduced CD16+ differentiation. Cytometry identified reduced CD16 expression in RA-BM monocytes and reduced frequencies of non-classical RA-PB monocytes, which confirmed transcriptome data. Comparing BM, blood and SF monocytes, a distinct intermediate-like but more activated population appeared only in the joint, which expressed high levels of both CD14 and CD16 along with increased levels of CD163 and HLA-DR. Shedded (sCD14 and sCD163) and released (S100P) markers of monocyte activation were also highest in RA SF and lower but still elevated in RA compared with OA serum.

These analyses indirectly suggest (1) an increased monocyte turnover, (2) reduced circulation time in the blood and (3) the most prominent activation of RA monocytes in the joints. This may have substantial implications for interpretation of pathomechanisms and for detection of biomarkers of disease activity or drug response.

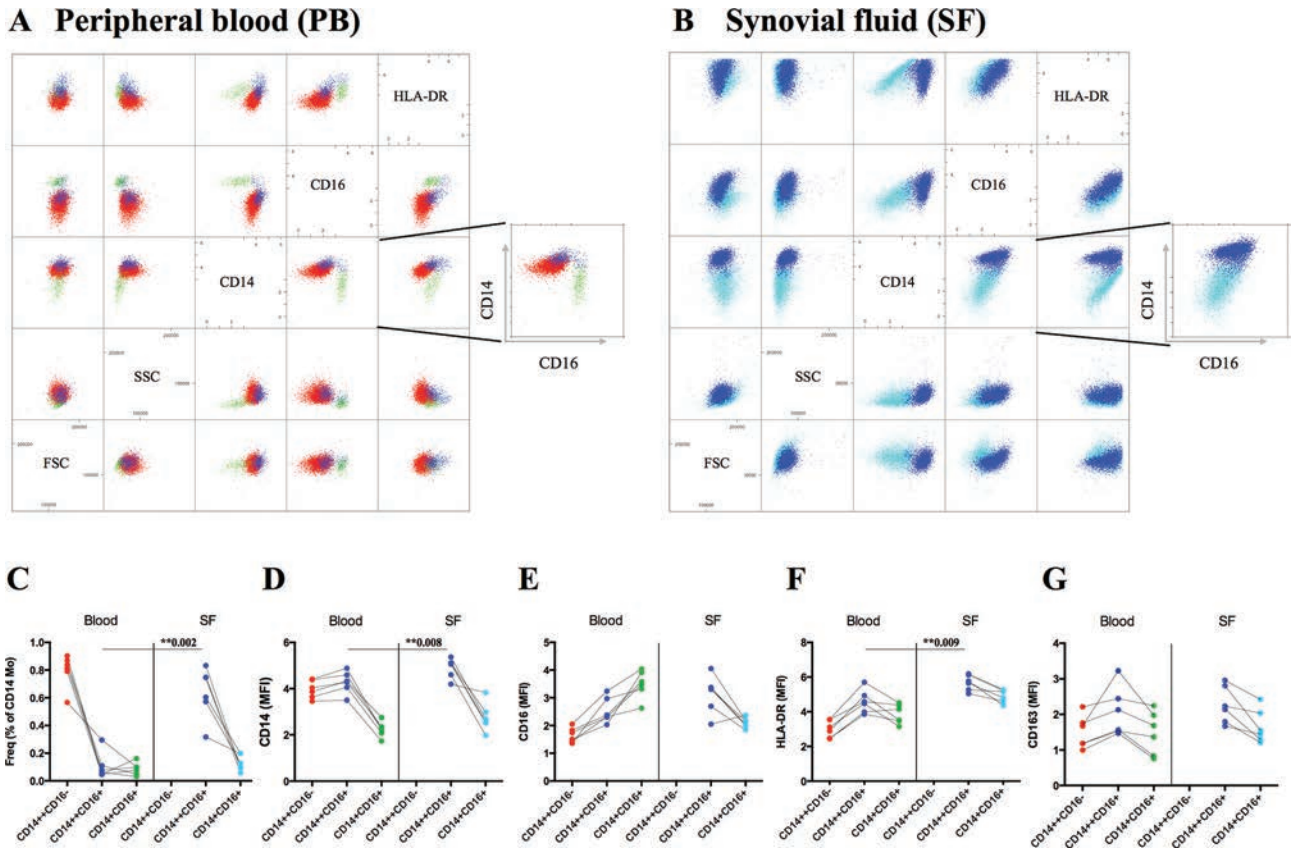


Figure 5 Cytometric analysis of monocyte subsets in blood and SF from patients with RA. Paired samples of blood and SF from six patients with RA were investigated for CD14, CD16 and HLA-DR expression. Scatterplot matrices from blood (A) and SF (B) samples of one representative patient demonstrate classical (CD14++CD16−; red), intermediate (CD14++CD16+; blue) and non-classical (CD14+CD16+; green) monocytes. In SF, monocytes with classical and non-classical CD14/CD16 pattern were absent, and ~20% of cells displayed myeloid phenotype (cyan). The dominant population in SF was similar to intermediate monocytes of blood but with increased CD14 and HLA-DR expression (significance determined by paired t-test was indicated with P value). Distribution of asinh-transformed mean fluorescence intensity (MFI) is presented for CD14 (D), CD16 (E), HLA-DR (F). Staining of CD163 with CD14 and CD16 was performed independent of HLA-DR, and thus it is not included in the scatterplot matrix, but it is shown in figure part G. RA, rheumatoid arthritis.

Transcriptome technology was applied in this study as comprehensive genome-wide approach in order to recognise the early and leading molecular mechanisms that affect BM and blood monocytes in RA. Comparison with reference transcriptomes revealed the most reliable and unambiguous results to identify the functional relevance of differentially expressed transcripts on a quantitative and technologically comparable level instead of literature-based annotations.

In detail, RA transcriptomes of BM and blood monocytes overlapped with signatures of precursors in myelopoietic differentiation, indicating a so-called 'left-shift'. Accelerated monocytopoiesis in RA-BM can be deduced from patterns increased in early (HSC, multipotent progenitors (MPP), megakaryocyte–erythrocyte progenitors (MEP), common myeloid progenitors (CMP), granulocyte–monocyte progenitors (GMP), early and late promyelocytes (PM) and MY) but reduced in late-stage myelopoiesis (MMs, band cells (BCs) and PMN cells and from increased G-CSF response patterns. 'Left-shift' in RA-PB monocytes is indicated by a largely extended G-CSF response pattern, which includes late stage myelopoiesis (MM, BC and PMN) as well as typical monocyte genes of the classical $CD16^-$ subset. Interestingly, development up to PMs still includes proliferation and subsequent stages more phagocytosis-related capabilities, suggesting that 'left-shift' in the BM is dominated by proliferation and in the blood by maturation processes.[33]

This accelerated monocytopoiesis is supported by earlier observations that RA haematopoietic precursors differentiate in vitro more rapidly into $CD14^+$ HLA-DR expressing monocytes than non-inflammatory controls.[34] Furthermore, cell anchoring during myelopoiesis to the BM matrix is mediated by integrins and their release by proteases.[35–38] In line with this concept, we showed that RA-BM monocytes expressed higher levels of integrins *ITGA4* and *ITGB1* like their early precursors and also elevated sheddase *ADAM10*, which is involved in their release from BM and also induced by G-CSF.[35 36 38] Egress of monocytes from BM was also associated with CCR2 activation and desensitisation of CXCR4 anchoring to BM stromal cells.[10 11 39] Both chemokine receptor transcripts were highly expressed on BM monocytes in both RA and OA. In line with a 'left-shift' in RA-PB monocytes, *CCR2* expression was increased in RA and decreased during differentiation from $CD14^+CD16^-$ to $CD14^+CD16^+$ subsets.[8 13 40] In contrast to RA, monocyte genes increased in OA overlapped with more differentiated progenitors in the BM and with a more differentiated subset of $CD16^+$ monocytes in the blood.

On this background, cytometry also reflected the 'left-shifted' monocytopoiesis by reduced CD16 expression on classical and intermediate monocytes in RA-BM when compared with OA. Additionally, the decreased frequency of non-classical $CD14^+CD16^+$ RA monocytes in blood indicated reduced

terminal differentiation in RA. Altogether, a 'left-shift' pattern and reduced differentiation in RA-PB raise the hypothesis of increased production, a shorter circulation time and faster migration into inflamed tissues. These conclusions are in line with cell tracking experiments in macaques, performed by in vivo BrdU staining, which is not possible in humans. These experiments demonstrated that lower CD14 expression on classical monocytes was related to younger cells and that the frequency of the terminally differentiated non-classical subset increased with circulation time.[9 41]

When investigating the joint compartment, the most obvious change was the absence of classical monocytes. The dominant population was similar to the intermediate phenotype of blood and revealed even further increase of HLA-DR, CD14 and CD163 expression compared with blood. As these markers were not different between RA and OA monocyte subsets in the blood, this indicates that activation occurred in the joint and that it was related to the intermediate subset. This is also emphasised by the high concentrations of shedded sCD14 and sCD163 and of released S100P in RA SF. The second population of $CD14^{+}CD16^{+}$ SF monocytes was small and may, according to the described phenotype, reflect differentiation towards typical tissue macrophages, which may not propagate activation and inflammation.

Recently, we demonstrated that response to MTX in RA is related to a predominance of innate immune activation.[42] Correspondingly, Ponchel *et al*[43] associated higher naïve T cell frequency with response to MTX. Thus, immunopathology of RA appears not independent of innate triggers and becomes more aggressive and difficult to treat when adaptive immune response gains dominance. Translating innate to adaptive immunity depends on monocytes, their activation by innate triggers, their antigen processing and presentation and their interaction with T cells. This might explain why combination of MTX with biologicals advances treatment of RA patients with reduced naïve T cells and more lymphocyte involvement.[43]

There is ongoing discussion about the primary site of RA initiation, which may occur either inside the joints or outside in organs, where immune cells develop (BM and lymph nodes) or interact with environment (gut, lung and gingiva).[44–46] Our results suggest that disease-specific triggering occurs in the joint, where search for biomarkers relevant for drug selection seems to be more promising. How and to what extent monocytes are triggered and, consequently, what is the magnitude of the innate and adaptive immune system activation seem to be essential to improve insight into RA aetiopathogenesis.

Acknowledgements We are grateful to Silvia Pade from the Department of Rheumatology at the Charité for sample and clinical data acquisition. For generating gene expression data, we are thankful to Heidi Schliemann and Heike Hirseland from the Regine-von-Ramin Laboratory of Molecular Rheumatology and to Neeraj Tandon from the Department of Rheumatology and Clinical Immunology, Charité Universitätsmedizin. We would also like to thank Toralf Kaiser and Jenny Kirsch from the core facility of flow cytometry and cell sorting at the German Rheumatism Research Centre for their excellent support in performing cell sorting experiments. We are thankful to Hans-Joachim Mollenkopf from the Max Plank Institute for Infectious Biology in Berlin for valuable discussion.

Contributors All authors meet the criteria for authorship. Conceived and designed the research: BiS, AG, AndR, WM, GRB and TH. Performed research: BiS, AnnR, EKW, WK, JRG, BrS and TH. Analysed data: BiS, AG, USW, TS and TH. Recruitment of patients and clinical investigation: AB, SH, SO, KA, MB and TH. Wrote the paper: BiS, AG, WM and TH.

Funding The work was supported by the European Union with the project AutoCure (LSHB-CT-2006-018861) and the IMI project Be The Cure (contract no 115142-2), the German Federal Ministry of Education and Research (BMBF) with the network project ArthroMark (01EC1009A) and the Deutsche Forschungs gemeinschaft (DFG) with the project SFB 650.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Institutional Ethics Committees in Poland and Germany approved this study.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Mitchell DM, Spitz PW, Young DY, *et al*. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986;29:706–14.
2 Zhang J, Chen L, Delzell E, *et al*. The association between inflammatory markers, serum lipids and the risk of cardiovascular events in patients with rheumatoid arthritis. *Ann Rheum Dis* 2014;73:1301–8.
3 Tacke F, Randolph GJ. Migratory fate and differentiation of blood monocyte subsets. *Immunobiology* 2006;211:609–18.
4 Ziegler-Heitbrock HW. Definition of human blood monocytes. *J Leukoc Biol* 2000;67:603–6.
5 Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. *Nat Rev Immunol* 2005;5:953–64.
6 Ziegler-Heitbrock L, Ancuta P, Crowe S, *et al*. Nomenclature of monocytes and dendritic cells in blood. *Blood* 2010;116:e74–e80.
7 Ginhoux F, Jung S. Monocytes and macrophages: developmental pathways and tissue homeostasis. *Nat Rev Immunol* 2014;14:392–404.
8 Ancuta P, Liu KY, Misra V, *et al*. Transcriptional profiling reveals developmental relationship and distinct biological functions of CD16+ and CD16- monocyte subsets. *BMC Genomics* 2009;10:403.
9 Sugimoto C, Hasegawa A, Saito Y, *et al*. Differentiation kinetics of blood monocytes and dendritic cells in macaques: insights to understanding human myeloid cell development. *J Immunol* 2015;195:1774–81.
10 Jung H, Mithal DS, Park JE, *et al*. Localized CCR2 activation in the bone marrow niche mobilizes monocytes by desensitizing CXCR4. *PLoS One* 2015;10:e0128387.
11 Serbina NV, Pamer EG. Monocyte emigration from bone marrow during bacterial infection requires signals mediated by chemokine receptor CCR2. *Nat Immunol* 2006;7:311–7.
12 Fantuzzi L, Borghi P, Ciolli V, *et al*. Loss of CCR2 expression and functional response to monocyte chemotactic protein (MCP-1) during the differentiation of human monocytes: role of secreted MCP-1 in the regulation of the chemotactic response. *Blood* 1999;94:875–83.
13 Liu B, Dhanda A, Hirani S, *et al*. CD14++CD16+ monocytes are enriched by glucocorticoid treatment and are functionally attenuated in driving effector T cell responses. *J Immunol* 2015;194:5150–60.
14 Smiljanovic B, Grün JR, Biesen R, *et al*. The multifaceted balance of TNF-α and type I/II interferon responses in SLE and RA: how monocytes manage the impact of cytokines. *J Mol Med* 2012;90:1295–309.
15 Rose T, Grützkau A, Hirseland H, *et al*. IFNα and its response proteins, IP-10 and SIGLEC-1, are biomarkers of disease activity in systemic lupus erythematosus. *Ann Rheum Dis* 2013;72:1639–45.
16 Stuhlmüller B, Häupl T, Hernandez MM, *et al*. CD11c as a transcriptional biomarker to predict response to anti-TNF monotherapy with adalimumab in patients with rheumatoid arthritis. *Clin Pharmacol Ther* 2010;87:311–21.
17 Cairns AP, Crockard AD, Bell AL. The CD14+ CD16+ monocyte subset in rheumatoid arthritis and systemic lupus erythematosus. *Rheumatol Int* 2002;21:189–92.
18 Rossol M, Kraus S, Pierer M, *et al*. The CD14(bright) CD16+ monocyte subset is expanded in rheumatoid arthritis and promotes expansion of the Th17 cell population. *Arthritis Rheum* 2012;64:671–7.
19 Yoon BR, Yoo SJ, Choi Y, *et al*. Functional phenotype of synovial monocytes modulating inflammatory T-cell responses in rheumatoid arthritis (RA). *PLoS One* 2014;9:e109775.
20 Chara L, Sánchez-Atrio A, Pérez A, *et al*. The number of circulating monocytes as biomarkers of the clinical response to methotrexate in untreated patients with rheumatoid arthritis. *J Transl Med* 2015;13:2.
21 Chara L, Sánchez-Atrio A, Pérez A, *et al*. Monocyte populations as markers of response to adalimumab plus MTX in rheumatoid arthritis. *Arthritis Res Ther* 2012;14:R175.
22 Aeberli D, Kamgang R, Balani D, *et al*. Regulation of peripheral classical and non-classical monocytes on infliximab treatment in patients with rheumatoid arthritis and ankylosing spondylitis. *RMD Open* 2016;2:e000079.

23 Mukherjee R, Kanti Barman P, Kumar Thatoi P, *et al*. Non-classical monocytes display inflammatory features: validation in sepsis and systemic lupus erythematous. *Sci Rep* 2015;5:13886.
24 Hamilton JA. Colony-stimulating factors in inflammation and autoimmunity. *Nat Rev Immunol* 2008;8:533–44.
25 Hamilton JA, Tak PP. The dynamics of macrophage lineage populations in inflammatory and autoimmune diseases. *Arthritis Rheum* 2009;60:1210–21.
26 Biesen R, Demir C, Barkhudarova F, *et al*. Sialic acid-binding Ig-like lectin 1 expression in inflammatory and resident monocytes is a potential biomarker for monitoring disease activity and success of therapy in systemic lupus erythematosus. *Arthritis Rheum* 2008;58:1136–45.
27 Smiljanovic B, Grün JR, Steinbrich-Zöllner M, *et al*. Defining TNF-α- and LPS-induced gene signatures in monocytes to unravel the complexity of peripheral blood transcriptomes in health and disease. *J Mol Med* 2010;88:1065–79.
28 Menssen A, Edinger G, Grün JR, *et al*. SiPaGene: a new repository for instant online retrieval, sharing and meta-analyses of genechip expression data. *BMC Genomics* 2009;10:98.
29 Kyogoku C, Smiljanovic B, Grün JR, *et al*. Cell-specific type I IFN signatures in autoimmunity and viral infection: what makes the difference? *PLoS One* 2013;8:e83776.
30 Sörensen T, Baumgart S, Durek P, *et al*. Immunoclust--an automated analysis pipeline for the identification of immunophenotypic signatures in high-dimensional cytometric datasets. *Cytometry A* 2015;87:603–15.
31 Maouche S, Poirier O, Godefroy T, *et al*. Performance comparison of two microarray platforms to assess differential gene expression in human monocyte and macrophage cells. *BMC Genomics* 2008;9:302.
32 Rapin N, Bagger FO, Jendholm J, *et al*. Comparing cancer vs normal gene expression profiles identifies new disease entities and common transcriptional programs in AML patients. *Blood* 2014;123:894–904.
33 Theilgaard-Mönch K, Jacobsen LC, Borup R, *et al*. The transcriptional program of terminal granulocytic differentiation. *Blood* 2005;105:1785–96.
34 Hirohata S, Yanagida T, Itoh K, *et al*. Accelerated generation of CD14+ monocyte-lineage cells from the bone marrow of rheumatoid arthritis patients. *Arthritis Rheum* 1996;39:836–43.
35 Lowin T, Straub RH. Integrins and their ligands in rheumatoid arthritis. *Arthritis Res Ther* 2011;13:244.
36 Isozaki T, Ishii S, Nishimi S, *et al*. A disintegrin and metalloprotease-10 is correlated with disease activity and mediates monocyte migration and adhesion in rheumatoid arthritis. *Transl Res* 2015;166:244–53.
37 Pruessmeyer J, Ludwig A. The good, the bad and the ugly substrates for ADAM10 and ADAM17 in brain pathology, inflammation and cancer. *Semin Cell Dev Biol* 2009;20:164–74.
38 Weber S, Wetzel S, Prox J, *et al*. Regulation of adult hematopoiesis by the a disintegrin and metalloproteinase 10 (ADAM10). *Biochem Biophys Res Commun* 2013;442:234–41.
39 Mandl M, Schmitz S, Weber C, *et al*. Characterization of the CD14++CD16+ monocyte population in human bone marrow. *PLoS One* 2014;9:e112140.
40 Frankenberger M, Hofer TP, Marei A, *et al*. Transcript profiling of CD16-positive monocytes reveals a unique molecular fingerprint. *Eur J Immunol* 2012;42:957–74.
41 McColgan P, Sharma P, Bentley P. Stem cell tracking in human trials: a meta-regression. *Stem Cell Rev* 2011;7:1031–40.
42 Stuhlmüller B, Mans K, Tandon N, *et al*. Genomic stratification by expression of HLA-DRB4 alleles identifies differential innate and adaptive immune transcriptional patterns - A strategy to detect predictors of methotrexate response in early rheumatoid arthritis. *Clin Immunol* 2016;171:50–61.
43 Ponchel F, Goëb V, Parmar R, *et al*. An immunological biomarker to predict MTX response in early RA. *Ann Rheum Dis* 2014;73:2047–53.
44 Schett G, Firestein GS. Mr Outside and Mr Inside: classic and alternative views on the pathogenesis of rheumatoid arthritis. *Ann Rheum Dis* 2010;69:787–9.
45 Malmström V, Catrina AI, Klareskog L. The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting. *Nat Rev Immunol* 2017;17:60–75.
46 Abdollahi-Roodsaz S, Abramson SB, Scher JU. The metabolic role of the gut microbiota in health and rheumatic disease: mechanisms and interventions. *Nat Rev Rheumatol* 2016;12:446–55.

Immunoscintigraphic detection of tumour necrosis factor by radiolabelled certolizumab pegol in patients with erosive hand osteoarthritis: a proof-of-concept study

Erosive hand osteoarthritis (OA) of the interphalangeal (IP) joints is characterised by a more pronounced inflammatory burden of disease.[1] Whether it is a subset of hand OA or just a radiographic phase remains a matter of debate. The pathogenesis of erosive OA is not yet understood, but articular cartilage degeneration and subchondral bone resorption are some of the major characteristics. In general, several cytokine-driven pathways such as receptor activator of nuclear factor κB, interleukin-1 and tumour necrosis factor (TNF) alpha are involved at the level of the subchondral bone-inducing dynamic morphological changes.[2–4] In post hoc analyses in two recent placebo-controlled pilot studies in erosive OA, it was shown that adalimumab and etanercept were able to diminish structural progression after 1 year of treatment in a subgroup of patients who showed soft tissue swelling at baseline.[5 6]

We hypothesised that radiolabelled antibodies could help in demonstrating their in vivo abundance in joints and help to identify joints at particular risk for progression amenable for targeted therapies.

The aim of the study was to assess the biodistribution of TNF in erosive OA and to identify the clinical features of the joints with most uptake.

Five patients with erosive hand OA (female:male ratio 4/1; median age 55.6 years; median disease duration 8.4 years) were intravenously injected with Tc^{99m}-radiolabelled certolizumab and static images of both hands were acquired immediately (early phase) and 4–6 hours postinjection (late phase).[7] Clinical assessments of the metacarpophalangeal and IP joints (presence of tenderness and soft tissue swelling (present/absent)) were performed. Immunoscintigraphic uptake of tracer was independently scored (absent/present). Approval of the local ethics committee and written and oral consent from the patient were obtained.

Descriptive statistics were calculated on joint level. No uptake was seen in any of the MCP joints and therefore these were excluded in further analyses.

The association between late TNF uptake (outcome) with clinical features (presence of tenderness and soft tissue swelling) (determinant) was studied by estimating crude ORs with 95% CIs using generalised estimating equations to account for the patient effect.

Tracer uptake was seen in late phase in 24 joints (26.7%). Example images are shown in figure 1.

Considerably more uptake was present in joints with soft tissue swelling compared with non-swollen joints: 14 (61.0%) of 23 swollen joints versus 10 (14.9%) of 67 non-swollen joints ($p<0.001$). Presence of soft tissue swelling was found to be significantly associated with uptake with OR of 8.9 (95% CI 3.0 to 26.0). A trend towards more uptake in tender joints was seen compared with non-tender joints (OR 2.1 (95% CI 0.8 to 5.6).

This study was the first to show the presence of TNF in erosive hand OA by immunoscintigraphy with radiolabelled TNF-blocking agents, here certolizumab. Uptake was present in almost 27% of IP joints. The strongest correlation was seen in joints with soft tissue swelling. In previous placebo-controlled clinical trials in erosive OA with TNF-blocking agents, it was demonstrated that presence of soft tissue swelling was the best predictor for preventing further erosive progression compared with placebo.[5 6] This study has some limitations: the sample size is low and a control group or another imaging construct is lacking.

The current observations indicate that TNF is contributing to the inflammatory burden of disease in erosive hand OA and presence of soft tissue swelling can help to risk-stratify patients amenable for future therapies.

Ruth Wittoek,[1] Philippe Carron,[1] Bieke Lambert,[2,3] Paulien Meersseman,[1] Gust Verbruggen,[1] Filip Van den Bosch,[1] Dirk Elewaut[1,4]

[1]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium
[2]Department of Radiology and Nuclear Medicine, Ghent University, Ghent, Belgium
[3]Department of Nuclear Medicine, AZ Maria Middelares, Ghent, Belgium
[4]VIB Inflammation Research Center, Ghent University Hospital, Ghent, Belgium

Correspondence to Dr Ruth Wittoek, Department of Rheumatology, Ghent University Hospital, De Pintelaan 185, Ghent B-9000, Belgium; ruth.wittoek@UGent.be

Acknowledgements The authors wish to thank the patients who participated in the study and Professor Filip De Vos (Laboratory of Radiopharmacy, Ghent University) for the radiolabelling of the molecule.

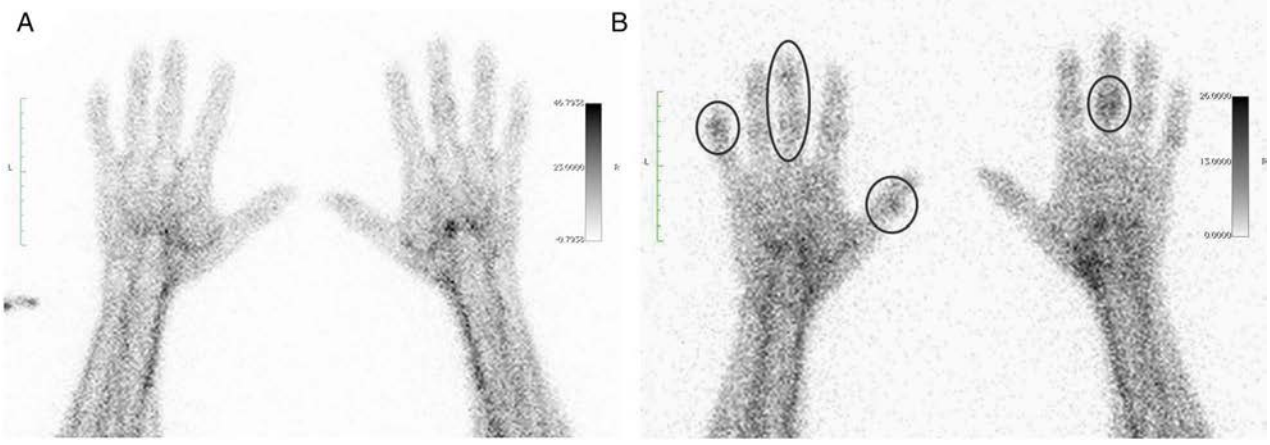


Figure 1 Early (A) and late (B) scintigraphic images showing uptake of ^{99m}Tc certolizumab. (A) Uptake in PIP3 joint of the right hand, becoming more clear in (B). (B) Also uptake in PIP3, IP1 and DIP3 and 5 in the left hand and PIP2 and DIP2 in the right hand.

Contributors Study design: RW, PC, BL, GV, FVdB, DE. Data collection: RW, PM, BL. Data analysis: RW. Data interpretation: RW, BL, PC, FVdB, DE. Writing of the report: RW. All authors approved the final version of the manuscript.

Funding This work concerns an investigator-initiated study supported by UCB Pharma.

Competing interests None.

Patient consent Obtained.

Ethics approval Ethics Committee of Ghent University Hospital, Belgium.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Wittoek R, Carron P, Lambert B, *et al*. *Ann Rheum Dis* 2018;**77**:310–311.

Received 12 August 2016
Revised 18 November 2016
Accepted 20 November 2016
Publishe Online First 8 December 2016

Ann Rheum Dis 2018;**77**:310–311. doi:10.1136/annrheumdis-2016-210354

REFERENCES

1 Punzi L, Frigato M, Frallonardo P, *et al*. Inflammatory osteoarthritis of the hand. *Best Pract Res Clin Rheumatol* 2010;24:301–12.
2 Lajeunesse D, Massicotte F, Pelletier JP, *et al*. Subchondral bone sclerosis in osteoarthritis: not just an innocent bystander. *Mod Rheumatol* 2003;13:7–14.
3 Kobayashi K, Takahashi N, Jimi E, *et al*. Tumor necrosis factor alpha stimulates osteoclast differentiation by a mechanism independent of the ODF/RANKL-RANK interaction. *J Exp Med* 2000;191:275–86.
4 Wei S, Kitaura H, Zhou P, *et al*. IL-1 mediates TNF-induced osteoclastogenesis. *J Clin Invest* 2005;115:282–90.
5 Verbruggen G, Wittoek R, Vander Cruyssen B, *et al*. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: a double blind, randomised trial on structure modification. *Ann Rheum Dis* 2012;71:891–8.
6 Kloppenburg M, Ramonda R, Kwok WY, *et al*. Randomized, placebo-controlled trial to evaluate clinical efficacy and structure modifying properties of subcutaneous etanercept (ETN) in patients with erosive inflammatory hand osteoarthritis. *Ann Rheum Dis* 2016;75(Suppl 2):90.
7 Carron P, Lambert B, Van Praet L, *et al*. Scintigraphic detection of TNF-driven inflammation by radiolabelled certolizumab pegol in patients with rheumatoid arthritis and spondyloarthritis. *RMD Open* 2016;2:e000265.

The EULAR points to consider for health professionals undertaking musculoskeletal ultrasound for rheumatic and musculoskeletal diseases

Musculoskeletal ultrasound has evolved into an important clinical decision-making tool by assisting in the diagnosis of inflammatory arthritis, monitoring disease activity and therapeutic response, and guiding interventions.[1–7] The role of the non-medical health professional has advanced, with many undertaking training and using musculoskeletal ultrasound to improve patient care and in doing so, increasing their scope of practice. Health professionals with clinical expertise and experience using ultrasound are also providing training for colleagues and medical clinicians.

As previously described among rheumatologists,[8 9] the use of musculoskeletal ultrasound and training undertaken varies significantly between different professional groups and across Europe. Guidelines to support training for rheumatologists have been formulated[10] but currently there are no recommendations to support the education and training needs of non-medical health professionals using musculoskeletal ultrasound.

A European League Against Rheumatism (EULAR) task force was established to reach a consensus on the role of, and education and training needs of health professionals undertaking musculoskeletal ultrasound for the management of people with rheumatic and musculoskeletal diseases (RMDs).

The group comprising of 18 clinical and academic experts representing 10 European countries included rheumatologists, nurses, physiotherapists, an epidemiologist, methodologist, radiologist, radiographer and podiatrist, and people with RMDs, who defined the aims and formulated 14 research questions to guide a comprehensive systematic literature search (SLR). The results of the SLR were discussed and supported the formulation of points to consider and a research agenda.

Table 1 Points to consider for health professionals undertaking musculoskeletal ultrasound for rheumatic and musculoskeletal diseases

Overarching principle
All health professionals may use musculoskeletal ultrasound, following appropriate training, within their scope of clinical practice and professional background

Points to consider	Category of evidence	Strength of statement	Level of agreement mean (95% CI)
Role and scope			
1. Health professionals may use ultrasound to detect musculoskeletal abnormalities and contribute to clinical decision-making.	3–4	D	9.2 (8.8 to 9.7)
2. Health professionals may use musculoskeletal ultrasound as a tool for research including health professional-led studies.	3–4	D	9.3 (8.7 to 9.9)
Training and competency			
3. Health professionals must be appropriately trained and assessed for competency in musculoskeletal ultrasound before applying it in clinical practice.	4	D	9.7 (9.5 to 10.0)
4. The minimal competency requirements for performing musculoskeletal ultrasound must be the same for all ultrasound practitioners. Advanced training content may be adapted according to the needs of the health professionals.	3–4	D	9.6 (9.2 to 10.0)
5. Health professionals appropriately trained may teach musculoskeletal ultrasound according to a standardised and formalised training programme.	4	D	9.5 (9.1 to 9.9)
Application and feasibility			
6. The use of musculoskeletal ultrasound by health professionals must be based on levels of competency and the individual's role within their institution/department, as directed by local and national regulations.	3–4	D	9.6 (9.4 to 9.9)
Additional value			
7. By using musculoskeletal ultrasound, health professionals may improve the clinical management of people with rheumatic and musculoskeletal diseases.	3–4	D	9.0 (8.3 to 9.7)

Box 1 Future research agenda

1. To determine the musculoskeletal ultrasound training needs of European League Against Rheumatism (EULAR) health professionals and how they intend to use ultrasound.
2. To develop a structured EULAR advanced musculoskeletal ultrasound training programme specific to the needs of health professionals.
3. To determine the provision of mentorship that health professionals will require to support their training needs in musculoskeletal ultrasound.
4. To understand the impact of health professionals performing musculoskeletal ultrasound on the care of people with rheumatic and musculoskeletal diseases.
5. To determine the cost effectiveness of models of care in which health professionals are using musculoskeletal ultrasound.
6. To determine and standardise the minimum requirements for reporting musculoskeletal ultrasound examinations performed by health professionals.
7. To evaluate the influence of the EULAR points to consider on the use of musculoskeletal ultrasound by health professionals.

Seven points to consider were formulated (table 1) encompassing the role and scope of health professionals using musculoskeletal ultrasound, including the application, feasibility and added value in daily practice, and the training and competencies required. The strength of the points to consider was rated D based on the category of evidence (3–4). A high level of agreement (range 9.0–9.7) was reached by the task force members. The task force agreed on seven topics for the research agenda (box 1).

These are the first points to consider produced by a EULAR task force for health professionals using musculoskeletal ultrasound. The task force acknowledged that there is weak evidence supporting the points to consider, which were developed using a combination of research-based evidence and expert consensus. The use of musculoskeletal ultrasound by health professionals in both clinical practice and research is increasing in popularity, hence these points to consider are timely. It is envisaged that they will need to be revisited as new evidence becomes available.

The seven points to consider are intended to support the education and training needs for health professionals using musculoskeletal ultrasound across Europe. It is important to note that these points to consider should be used in conjunction with local and national regulations. There was consensus that the role and scope of ultrasound practice for non-medical sonographers does not differ significantly from that applying to rheumatologists, and therefore the training and competency levels should be the same for rheumatologists and health professionals using musculoskeletal ultrasound in clinical practice and for research.

A full description of the SLR and points to consider development are available at http://www.eular.org.

Heidi J Siddle,[1,2] Peter Mandl,[3] Daniel Aletaha,[3] Thea P Vliet Vlieland,[4] Marina Backhaus,[5] Patricia Cornell,[6] Maria-Antonietta D'Agostino,[1,7] Karen Ellegaard,[8] Annamaria Iagnocco,[9] Bente Jakobsen,[10] Tiina Jasinski,[11] Nina H Kildal,[12] Michaela Lehner,[3] Ingrid Möller,[13] Gabriela M Supp,[3] Philip O'Connor,[2,14] Anthony C Redmond,[1,2] Esperanza Naredo,[15] Richard J Wakefield[1,2]

[1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK
[2]NIHR Leeds Musculoskeletal Biomedical Research Centre, Leeds, UK
[3]Division of Rheumatology, Medical University of Vienna, Vienna, Austria
[4]Department of Orthopaedics, Rehabilitation and Physical Therapy, Leiden University Medical Centre, Leiden, The Netherlands
[5]Department of Internal Medicine, Rheumatology and Clinical Immunology, Academic Hospital of the Charité Berlin, Berlin, Germany
[6]Department of Rheumatology, Poole Hospital NHS Foundation Trust, Poole, UK
[7]Laboratoire d'Excellence INFLAMEX, Versailles-Saint-Quentin University, Saint-Quentin en Yvelines, France
[8]The Parker Institute, Copenhagen University Hospital Bispebjerg-Frederiksberg, Copenhagen, Denmark
[9]Rheumatology Unit—Dipartimento di Medicina Interna e Specialità Mediche, Sapienza Università di Roma, Rome, Italy
[10]National Advisory Unit on Pregnancy and Rheumatic Diseases, St. Olavs Hospital, Trondheim, Norway
[11]Patient Research Partner, Estonian Rheumatism Association, Tallinn, Estonia
[12]Faculty of Health and Social Science, Norwegian University of Science and Technology, Trondheim, Norway
[13]Instituto Poal de Reumatologia, Barcelona, Spain
[14]Department of Radiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[15]Department of Rheumatology, Hospital GU Gregorio Marañón, Madrid, Spain

Correspondence to Dr Heidi J Siddle, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Chapeltown Road, Leeds LS7 4SA, UK; h.siddle@leeds.ac.uk

Acknowledgements The authors thank Sue Oliver, OBE for her leadership in the conception of this project. The authors also thank Deirdre Andre, Scholarly Communications and Research Skills Advisor, Leeds University Library for her support in conducting the systematic literature review.

Contributors HJS was the research fellow for the project, undertaking the SLR. RJW was the project convener; PM, DA and TPVV provided epidemiology direction for the SLR and the project. HJS and RJW were responsible for drafting the manuscript. All those listed as authors were responsible for developing the points to consider and reading, commenting on, and approving the final manuscript. All contributors were independent from the study funders in conducting the research.

Funding This project was supported by the European League Against Rheumatism (EULAR). The research is supported by the National Institute for Health Research (NIHR) Leeds Musculoskeletal Biomedical Research Centre, UK. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Siddle HJ, Mandl P, Aletaha D, *et al*. *Ann Rheum Dis* 2018;**77**:311–313.

Received 28 October 2016
Accepted 22 November 2016
Publishe Online First 9 December 2016

Ann Rheum Dis 2018;**77**:311–313. doi:10.1136/annrheumdis-2016-210741

REFERENCES

1 Wakefield RJ, Gibbon WW, Conaghan PG, *et al*. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. *Arthritis Rheum* 2000;43:2762–70.
2 Karim Z, Wakefield RJ, Conaghan PG, *et al*. The impact of ultrasonography on diagnosis and management of patients with musculoskeletal conditions. *Arthritis Rheum* 2001;44:2932–3.
3 Terslev L, Torp-Pedersen S, Savnik A, *et al*. Doppler ultrasound and magnetic resonance imaging of synovial inflammation of the hand in rheumatoid arthritis: a comparative study. *Arthritis Rheum* 2003;48:2434–41.
4 d'Agostino MA, Ayral X, Baron G, *et al*. Impact of ultrasound imaging on local corticosteroid injections of symptomatic ankle, hind-, and mid-foot in chronic inflammatory diseases. *Arthritis Rheum* 2005;53:284–92.
5 Brown AK, Quinn MA, Karim Z, *et al*. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study May explain structural progression. *Arthritis Rheum* 2006;54:3761–73.

6 Koski JM, Saarakkala S, Helle M, *et al*. Assessing the intra- and inter-reader reliability of dynamic ultrasound images in power Doppler ultrasonography. *Ann Rheum Dis* 2006;65:1658–60.
7 Naredo E, Collado P, Cruz A, *et al*. Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: predictive value in disease activity and radiologic progression. *Arthritis Rheum* 2007;57:116–24.
8 Naredo E, D'Agostino MA, Conaghan PG, *et al*. Current state of musculoskeletal ultrasound training and implementation in Europe: results of a survey of experts and scientific societies. *Rheumatology (Oxford)* 2010;49:2438–43.
9 Mandl P, Naredo E, Conaghan PG, *et al*. Practice of ultrasound-guided arthrocentesis and joint injection, including training and implementation, in Europe: results of a survey of experts and scientific societies. *Rheumatology (Oxford)* 2012;51:184–90.
10 Terslev L, Hammer HB, Torp-Pedersen S, *et al*. EFSUMB minimum training requirements for rheumatologists performing musculoskeletal ultrasound. *Ultraschall Med* 2013;34:475–7.

Plasma oxypurinol as a measure of adherence in clinical trials

Adherence to urate-lowering therapy (ULT) in people with gout is often poor. A recent systematic review revealed 10%–46% of people with gout adhere to treatment.[1] Among chronic diseases, gout has particularly low adherence rates.[2] Adherence in clinical trials of ULT is a particularly important issue, as the primary efficacy endpoint for most studies (including phase III studies that form the basis of regulatory approval) is the ability of the agent to reduce serum urate (SU). Pill count-based adherence ≥80% is frequently regarded as an appropriate cut-off for good adherence; however, this is an indirect measure. Measurement of drug concentration may be an improved measure of the adherence.[3] The aim of this study was to establish the relationship between two different measures of adherence and SU endpoints in a clinical trial of allopurinol in gout.

Data, including demographics, SU, estimated glomerular filtration rate (eGFR), and plasma oxypurinol and allopurinol concentrations were available from a single study visit, and cumulative pill counts from the entire study period were available for 395 participants in the Long-term Allopurinol Safety Study Evaluating Outcomes in Gout Patients study (NCT01391325).[4] At each study visit, prescription allopurinol tablets were counted and dispensed back to the patient, and pill counts were recorded. Pill counts ≥80% over the entire study period were taken as indicating good adherence. Plasma oxypurinol and allopurinol were measured as previously described.[5] Allopurinol concentrations >0 were taken to indicate that the participant had taken allopurinol within a few hours of the study visit, while oxypurinol concentrations >20 μmol/L were taken to indicate adherence over the preceding days to weeks.

For the 395 participants, the mean (SD) age was 51.2 (11.1), mean (SD) body mass index (BMI) was 35.4 (7.8), 94.4% were male, 13.2% had tophi, 19.2% were receiving a diuretic and mean (SD) eGFR was 79.3 (19.9) mL/min/1.73 m^2. Pill counts ≥80% were recorded in 357/395 (90.4%) participants. Those with pill counts ≥80% had lower SU and higher plasma oxypurinol and allopurinol concentrations compared with those with pill counts <80% (table 1). Pill counts and allopurinol doses were not different between those with plasma oxypurinol of 0 μmol/L, 0–<20 μmol/L or ≥20 μmol/L (table 1). Of the 19 participants with undetectable plasma oxypurinol, 16 (84%) had pill counts ≥80%. In the 357 participants with pill counts ≥80%, plasma oxypurinol concentrations were significantly higher in those with SU<6 mg/dL (0.36 mmol/L) compared with those with SU >6 mg/dL ((mean (SD) oxypurinol 94.5 (43.2) μmol/L vs 67.2 (51.2) μmol/L; p<0.001)). In a multivariate logistic regression analysis including age and BMI, plasma oxypurinol was a significant independent predictor of achieving SU<6 mg/dL (0.36 mmol/L) (OR 1.14; 95% CI 1.08 to 1.20 per 10 μmol/L) (table 2). Pill counts were not a significant independent predictor of SU<6 mg/dL (0.36 mmol/L) (OR 1.1; 95% CI 0.94 to 1.3 per 10% increment pill count).

These data suggest that pill counts may not be a reliable measure of adherence in clinical trials of ULT and that adding drug concentration leads to more accurate assessment of adherence. It is possible that those with low oxypurinol concentrations were adherent but had increased oxypurinol clearance or poor absorption.[6] The most likely explanation for undetectable or low plasma oxypurinol concentrations is low adherence. Importantly, pill counts and plasma oxypurinol provide information about adherence over different time frames, for monthly pill counts over the preceding month and for oxypurinol over the preceding days to weeks.[3]

Our data suggest that plasma oxypurinol is an appropriate measure of adherence in clinical trials of allopurinol and is superior to pill counts. New clinical trials of ULT need to carefully consider the most appropriate measure of adherence and how adherence should be reported.

Table 1 Comparison of participants with pill counts above and below 80% and at different oxypurinol concentrations

	Pill counts <80% (n=38)	Pill counts ≥80% (n=357)	p Value	Oxypurinol=0 (n=19)	Oxypurinol >0 to <20 (n=13)	Oxypurinol ≥20 (n=363)	p Value
Allopurinol dose, mg/day, mean (SD)	314.5 (103.3)	310.4 (74.9)	0.76	294.7 (91.1)	284.6 (55.5)	312.8 (77.9)	0.29
Serum urate mg/dL, mean (SD)	6.9 (1.5)	6.0 (1.3)	0.003	9.07 (2.0)	7.6 (1.2)	6.0 (1.2)	<0.001
Serum urate mmol/L mean (SD)	0.41 (0.09)	0.36 (0.08)		0.54 (0.11)	0.43 (0.07)	0.36 (0.07)	
Serum urate <6 mg/dL (0.36 mmol/L), n (%)	11 (28.9)	187 (52.4)	0.006	0	1 (7.7)	197 (54.3)	<0.001
Plasma oxypurinol μmol/L, mean (SD)	64.8 (41.2)	81.5 (49.1)	0.04	0 (0)	9.2 (6.4)	86.6 (44.8)	<0.001
Plasma oxypurinol mg/L, mean (SD)	9.9 (6.3)	12.4 (7.5)					
Plasma allopurinol >0 μmol/L, n (%)	9 (23.7)	162 (45.4)	0.010	0 (0)	1 (7.7)	170 (46.8)	<0.001
Plasma oxypurinol, n (%)							
0 μmol/L	3 (7.9)	16 (4.8)	0.49				
>0–≤20 μmol/L	2 (5.3)	11 (3.1)					
>20 μmol/L	33 (86.8)	330 (92.4)					
Pill counts %, mean (SD)				92.8 (15.3)	91.9 (12.3)	95.8 (14.2)	0.44
Diuretic use, n (%)	9 (23.7)	67 (18.8)	0.47	4 (21.1)	0 (0.0)	72 (19.8)	0.49

Table 2 Factors associated with serum urate above and below target (6 mg/dL)

	Urate <6 mg/dL (n=198)	Urate ≥6 mg/dL (n=197)	p Value
Age, years, mean (SD)	53.0 (10.6)	49.4 (11.4)	0.001
Male, n (%)	187 (94.4)	186 (94.4)	0.99
Tophi, n (%)	26 (13.1)	26 (13.2)	0.98
Diuretic use, n (%)	32 (16.2)	44 (22.3)	0.12
eGFR mL/min/1.73 m^2, mean (SD), mean (SD)	78.5 (18.4)	80.1 (21.5)	0.42
BMI kg/m^2, mean (SD)	34.1 (7.0)	36.7 (8.3)	0.001
Pill counts, %, mean (SD)	97.0 (13.2)	93.9 (15.0)	0.03
Plasma oxypurinol, μmol/L, mean (SD)	93. 3 (42.9)	66.5 (50.3)	<0.001
Plasma oxypurinol, mg/L mean (SD)	14.3 (6.5)	10.1 (7.7)	
Plasma allopurinol, μmol/L, mean (SD)	3.8 (5.2)	2.1 (3.9)	<0.001
Plasma allopurinol, mg/L, mean (SD)	0.5 (0.7)	0.3 (0.5)	
Serum urate, mg/dL, mean (SD)	5.2 (0.6)	7.2 (1.2)	<0.001
Serum urate, mmol/L, mean (SD)	0.31 (0.004)	0.43 (0.07)	
Allopurinol dose, mg/day, mean (SD)	314.4 (69.5)	307.1 (85.7)	0.35
Multivariate analysis	**Adjusted OR (95% CI)**	**p Value**	
Age per decade	1.09 (0.90 to 1.34)	0.39	
BMI	0.95 (0.02 to 0.98)	0.001	
Plasma oxypurinol concentration per 10 μmol/L	1.14 (1.08 to 1.20)	<0.001	
Pill counts per 10% increment	1.10 (0.94 to 1.28)	0.21	

The base model included age and BMI as independent predictors of achieving serum urate <6 mg/dL.
BMI, body mass index; eGFR, estimated glomerular filtration rate.

Lisa K Stamp,[1] Tony Merriman,[2] Christopher Frampton,[1] Mei Zhang,[1,3] Mary Wallace,[4] Jeffrey N Miner,[5] Nicola Dalbeth[6]

[1]Department of Medicine, University of Otago, Christchurch, Christchurch, New Zealand
[2]Department of Biochemistry, University of Otago, Dunedin, New Zealand
[3]Department of Toxicology, Canterbury Health Laboratories, Christchurch, New Zealand
[4]Deparment of Surgery, University of Otago, Dunedin, New Zealand
[5]Biology Department, Ardea Biosciences, Inc., San Diego, California, USA
[6]Deparment of Medicine, University of Auckland, Auckland, New Zealand

Correspondence to Professor Lisa Stamp, Department of Medicine, University of Otago, Christchurch, P. O. Box 4345 Christchurch 8140, New Zealand; lisa.stamp@cdhb.health.nz

Funding This work was funded by Ardea Biosciences, a member of the AstraZeneca group.

Contributors LKS—conception and design of the work, analysis and interpretation of data, drafting the work and final approval. TM—conception and design of the work, interpretation of data and final approval. CF—design, data analysis, manuscript approval. MZ—design, data acquisition, interpretation of data, final approval. MW—design of the work, data acquisition, analysis and interpretation of data, drafting the work and final approval. JNM—conception and design of the work, interpretation of data, drafting the work and final approval. ND—conception and design of the work, analysis and interpretation of data, drafting the work and final approval.

Competing interests LKS reports grant funding from Ardea Biosciences related to the current work. TM reports grant funding from Ardea Biosciences related to the current work and grant funding from Ardea Biosciences outside the related work. JNM is the employee of Ardea Biosciences (a member of the AstraZeneca group) and shareholder of AstraZeneca Stock. ND reports consultancy from Ardea Biosciences related to the current work, and grant funding, consultancy or speaker fees from Takeda, Teijin, Menarini, Pfizer, Ardea Biosciences/AstraZeneca, Cymabay and Crealta all outside the submitted work.

Patient consent Obtained.

Ethics approval Ethical approval was received from The New Zealand Multiregional Ethics Committee (MEC05/10/130) and in the USA Schulman Central IRB (201102890) and NTY/11/07/074.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Stamp LK, Merriman T, Frampton C, *et al*. *Ann Rheum Dis* 2018;**77**:313–314.

Received 9 October 2016
Revised 15 December 2016
Accepted 17 December 2016
Publishe Online First 5 January 2017

Ann Rheum Dis 2018;**77**:313–314. doi:10.1136/annrheumdis-2016-210661

REFERENCES

1 De Vera M, Marcotte G, Rai S, *et al*. Medication adherence in gout: a systematic review. *Arthritis Care Res* 2014;66:1551–9.
2 Briesacher BA, Andrade S, Fouayzi H, *et al*. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy* 2008;28:437–43.
3 Vrijens B, Urquhart J. Methods for measuring, enhancing, and accounting for medication adherence in clinical trials. *Clin Pharmacol Ther* 2014;95:617–26.
4 Becker M, Fitz-Patrick D, Choi H, *et al*. An open-label, 6-month study of allopurinol safety in gout: The LASSO study. *Semin Arthritis Rheum* 2015;45:174–83.
5 Stamp LK, O'Donnell JL, Zhang M, *et al*. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. *Arthritis Rheum* 2011;63:412–21.
6 Stamp LK, Merriman TR, Barclay ML, *et al*. Impaired response or insufficient dosage? Examining the potential causes of "inadequate response" to allopurinol in the treatment of gout. *Semin Arthritis Rheum* 2014;44:170–4.

Eplerenone treatment alleviates the development of joint lesions in a new rat model of spontaneous metabolic-associated osteoarthritis

Increasing epidemiological and clinical studies suggest that metabolic syndrome (MetS) plays a role in the incidence and progression of osteoarthritis (OA).[1 2] However, in absence of an appropriate MetS-associated OA experimental model,[3] the MetS contribution to the joint phenotype in OA remains difficult to investigate and the evaluation of potential disease-modifying OA drugs (DMOADs) is complicated. Noteworthy, in contrast to their lean SHHF$^{+/+}$(spontaneously hypertensive heart failure) controls, obese SHHF$^{cp/cp}$ rats, a well-characterised model of MetS,[4] develop drastic metabolic, cardiovascular and renal alterations that are substantially improved through an early chronic mineralocorticoid receptor antagonism (MRA) treatment.[5] Thus, by comparing young (1.5 months) and aged (12.5 months) lean SHHF$^{+/+}$ and obese SHHF$^{cp/cp}$ rats, we sought to evaluate for the first time the potential (1) contribution of MetS to joint alterations and (2) therapeutic benefits derived from chronic MRA treatment by eplerenone (figure 1A).

Rats with no MetS ($^{1.5}$SHHF$^{+/+}$ and $^{12.5}$SHHF$^{+/+}$) or with barely developed MetS ($^{1.5}$SHHF$^{cp/cp}$)[4] displayed normal knee articular phenotype (figure 1Ba,e,i,m and data not shown for young rats). In striking contrast, $^{12.5}$SHHF$^{cp/cp}$ rats, affected by culminating MetS conditions,[5] exhibited knee joints with marked fibrillations from the surface to the middle layer of the cartilage (figure 1B\c,g,k) and moderate to severe loss of proteoglycans (figure 1Bg) and collagen II (figure 1Bk) through the entire thickness of the cartilage. These alterations of the $^{12.5}$SHHF$^{cp/cp}$ knees were associated with pronounced osteophyte formation (figure 1Bc,k) and with fibrosis, inflammation and cellular infiltration of the synovial tissue (figure 1Bc,o). Very interestingly, we could demonstrate that a preventive 11-month eplerenone treatment did not alter the normal knee

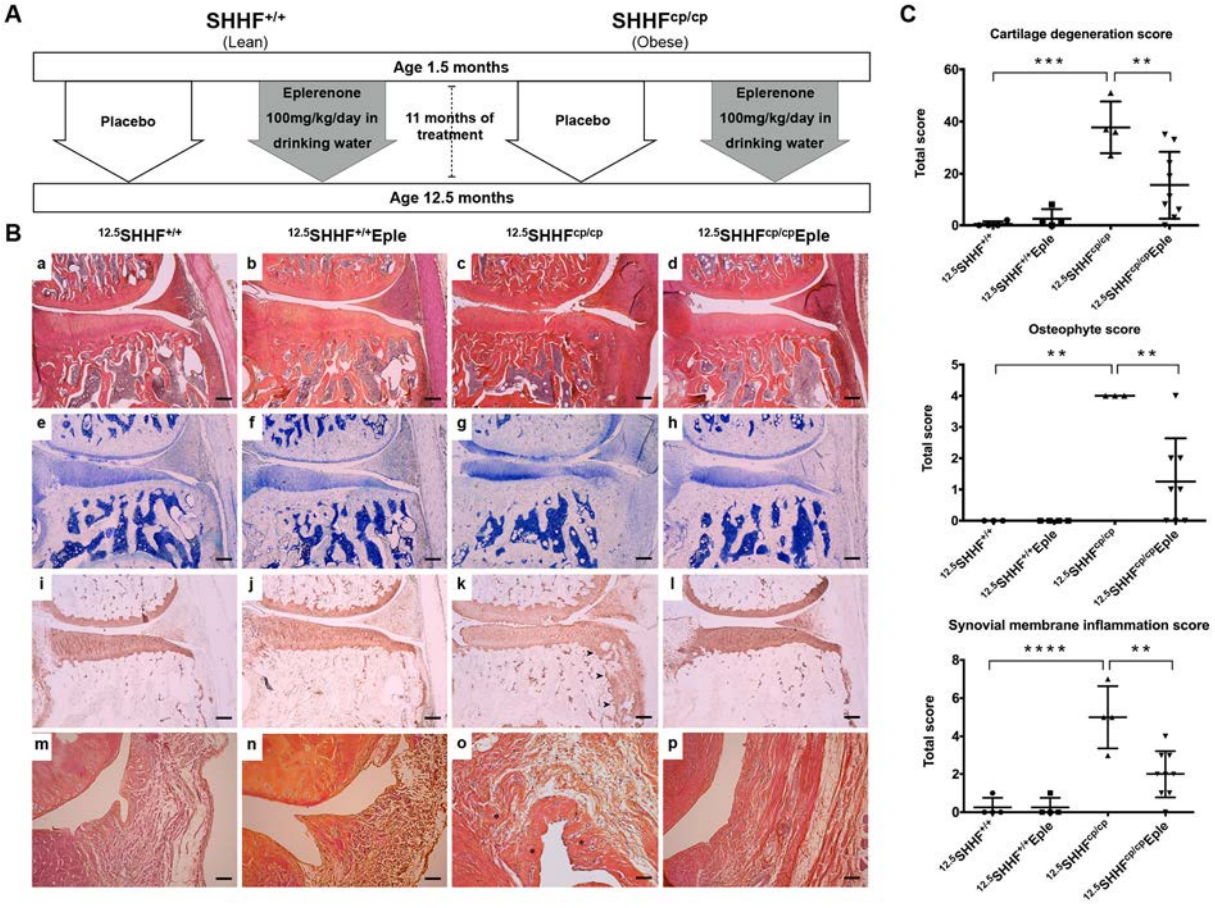


Figure 1 Preventive 11-month treatment with mineralocorticoid receptor antagonist eplerenone alleviated the metabolic syndrome (MetS)-associated joint lesions in SHHF model. (A) Experimental design of the study. Lean spontaneously hypertensive heart failure (SHHF$^{+/+}$) and obese SHHF$^{cp/cp}$ rats were divided randomly into treatment groups. Untreated groups (n=4 for SHHF$^{+/+}$ and n=4 for SHHF$^{cp/cp}$) were given placebo and Eple groups (n=4 for SHHF$^{+/+}$ and n=9 for SHHF$^{cp/cp}$) were given 100 mg/kg/day of eplerenone (gift from Pfizer) in drinking water from 1.5 months to 12.5 months of age. Knee joints of 1.5-month-old and 12.5-month-old specimens of each group were collected for histological analysis. (B) Representative H&E staining (a–d, m–p), toluidine blue staining (e–h) and collagen II immunohistochemistry (i–l) sections of the knee joint of $^{12.5}$SHHF$^{+/+}$, $^{12.5}$SHHF$^{+/+}$Eple, $^{12.5}$SHHF$^{cp/cp}$ and $^{12.5}$SHHF$^{cp/cp}$Eple rats. In panel k, the arrowheads demarcate osteophyte. In panel o, the arrows point to the infiltration and the asterisks indicate area of fibrosis. Scale bar: 100 µm for magnification ×4 (a–l) and 20 µm for magnification ×20 (m–p). (C) Scores for cartilage degradation, osteophyte formation and synovial membrane inflammation in $^{12.5}$SHHF$^{+/+}$, $^{12.5}$SHHF$^{+/+}$Eple, $^{12.5}$SHHF$^{cp/cp}$ and $^{12.5}$SHHF$^{cp/cp}$Eple rats were performed blindly by at least two independent investigators according to OARSI recommendations.[6] Values represent mean±SD. One-way ANOVA with Bonferroni's correction was used for statistical analysis, **p<0.01, ***p<0.001, ****p<0.0001.

phenotype of $^{12.5}$SHHF$^{+/+}$ rats (figure 1Bb,f,j,n) but substantially reduced the cartilage damages, osteophyte formation and synovial inflammation observed in placebo $^{12.5}$SHHF$^{cp/cp}$ rats (compare figure 1Bd,h,l,p with figure 1Bc,g,k,o, respectively). These striking findings were further substantiated by cartilage degeneration, osteophyte formation and synovial membrane inflammation scores, measured according to the lastest OARSI (Osteoarthritis Research Society International) recommendations for histological assessments in rats[6] (figure 1C). Altogether, this establishes that metabolic disorders in obese SHHF$^{cp/cp}$ rats induce changes in the knee joint that are significantly prevented on chronic treatment with MRA eplerenone.

Stratifying OA of various aetiologies to attain precision medicine[7] is yet of limited interest as no efficient and specific DMOAD is available for clinical use.[3 7] In this regard, the present pilot study sustains the proof of concept that preventive and chronic MRA treatment with the well known safety profile drug eplerenone may constitute a promising therapeutic strategy effective for patients with MetS at increased risk of developing knee OA, especially those with abdominal obesity we very recently reported to be better responders to eplerenone.[8] Interestingly, through the known beneficial impact of eplerenone on cardiac[5] and renal (unpublished data) conditions, plus the hereby supported positive effect on the development of MetS-associated cartilage and synovial lesions, MRA could ease mobility of this subfamily of patients with OA. If validated in clinic, such improvement of their life quality might further participate to the decrease of cardiovascular risks in patients with MetS by maintaining physical activity.

In conclusion, we uncovered the SHHF$^{cp/cp}$ strain as a unique spontaneous MetS-associated OA model in rat. Although the bone phenotype remains to be characterised, our work highlights the SHHF model as a novel and attractive instrumental tool to evaluate new preventive and curative therapeutics. Actually, using this model, we evidenced that preventive chronic MRA could positively impede the development of OA-like lesions in the articular and synovial tissues of individuals with MetS. Current and future investigations in vitro, in SHHF models and in patients cohorts will help decipher which and how systemic and/or local modulations of MR-downstream pathways[9] are involved in this uncovered beneficial effect of eplerenone in MetS-induced OA lesions.

Chaohua Deng,[1,2] Arnaud Bianchi,[1,2] Nathalie Presle,[1,2] David Moulin,[1,2,3] Meriem Koufany,[1,2] Cécile Guillaume,[1,2] Hervé Kempf,[1,2] Anne Pizard[2,3,4,5]

[1]UMR7365 CNRS-Université de Lorraine, IMoPA, Ingénierie Moléculaire et Physiopathologie Articulaire, Vandoeuvre-les-Nancy, France
[2]Fédération de Recherche 3209, Vandoeuvre-les-Nancy, France
[3]CHRU Nancy, Vandoeuvre-les-Nancy, France
[4]CIC-P1433 Inserm, CHRU Nancy, Vandoeuvre-les-Nancy, France
[5]UMRS-Inserm U1116, Université de Lorraine, Vandoeuvre-les-Nancy, France

Correspondence to Dr Hervé Kempf, UMR 7365 CNRS-UL, IMoPA, 9 avenue de la Forrêt de Haye, Vandoeuvre-lès-Nancy 54500, France; herve.kempf@inserm.fr and Dr Anne Pizard, UMRS-Inserm U1116, CHRU Nancy, ILCV, 4 rue du Morvan, Vandoeuvre-les-Nancy 54500, France; anne.pizard@inserm.fr

Correction notice This article has been corrected since it published Online First. The joint author statement for AP and HK has been added and the order of the authors updated.

Collaborators AP and HK are joint senior authors.

Contributors HK and AP conceived the study. CD, AB, NP, DM, MK, CG and AP performed the experiments. CD, AB, NP, DM, MK, HK and AP interpreted the data. CD, HK and AP wrote the manuscript.

Funding This work was supported by Inserm and Région Lorraine. CD was funded by a China Scholarship Council graduate scholarship.

Disclaimer The sponsors had no role in any experimental part of the study or the writing of the manuscript.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

HK and AP both contributed equally as senior authors.

To cite Deng C, Bianchi A, Presle N, *et al*. *Ann Rheum Dis* 2018;**77**:315–316.

Received 20 October 2016
Revised 26 February 2017
Accepted 29 March 2017
Published Online First 18 September 2017

Ann Rheum Dis 2018;**77**:315–316. doi:10.1136/annrheumdis-2016-210700

REFERENCES

1 Zhuo Q, Yang W, Chen J, *et al*. Metabolic syndrome meets osteoarthritis. *Nat Rev Rheumatol* 2012;8:729–37.
2 Berenbaum F, Griffin TM, Liu-Bryan R. Review: metabolic regulation of inflammation in osteoarthritis. *Arthritis Rheumatol* 2017;69:9–21.
3 Courties A, Gualillo O, Berenbaum F, *et al*. Metabolic stress-induced joint inflammation and osteoarthritis. *Osteoarthritis Cartilage* 2015;23:1955–65.
4 Youcef G, Olivier A, L'Huillier CP, *et al*. Simultaneous characterization of metabolic, cardiac, vascular and renal phenotypes of lean and obese SHHF rats. *PLoS One* 2014;9:e96452.
5 Youcef G, Olivier A, Nicot N, *et al*. Preventive and chronic mineralocorticoid receptor antagonism is highly beneficial in obese SHHF rats. *Br J Pharmacol* 2016;173:1805–19.
6 Gerwin N, Bendele AM, Glasson S, *et al*. The OARSI histopathology initiative - recommendations for histological assessments of osteoarthritis in the rat. *Osteoarthritis Cartilage* 2010;18:24–34.
7 Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011;377:2115–26.
8 Olivier A, Pitt B, Girerd N, *et al*. Effect of eplerenone in patients with heart failure and reduced ejection fraction: potential effect modification by abdominal obesity: insight from the EMPHASIS-HF trial. *Eur J Heart Fail* 2017.
9 Jaisser F, Farman N. Emerging roles of the mineralocorticoid receptor in pathology: toward new paradigms in clinical pharmacology. *Pharmacol Rev* 2016;68:49–75.

Ustekinumab inhibits Th1 and Th17 polarisation in a patient with giant cell arteritis

Although glucocorticoids (GC) remain the corner stone of giant cell arteritis (GCA) treatment, GC-sparing strategies are needed because GC are responsible for side effects.[1] Recent advances in the pathophysiology of GCA showed that CD4+ T cells are recruited in the arterial wall and polarised into Th1 and Th17 cells,[2 3] the latter being sensitive to GC-mediated suppression, whereas Th1 response persists in GC-treated patients,[2] which triggers the recruitment of macrophages[4] and could be implicated in the occurrence of relapses when GC are tapered. Interleukin (IL)-12 and IL-23 are two cytokines involved in Th1 and Th17 polarisations, respectively.[5] These two cytokines share a common subunit (p40), which allows ustekinumab, a humanised anti-p40 monoclonal antibody, to target both IL-12 and IL-23 pathways, thus disrupting in theory Th1 and Th17 immune responses.[6] Recently, an open-label study reported on the efficacy and safety of ustekinumab in 14 patients with refractory GCA[7] but data about T-cell polarisation were not available.

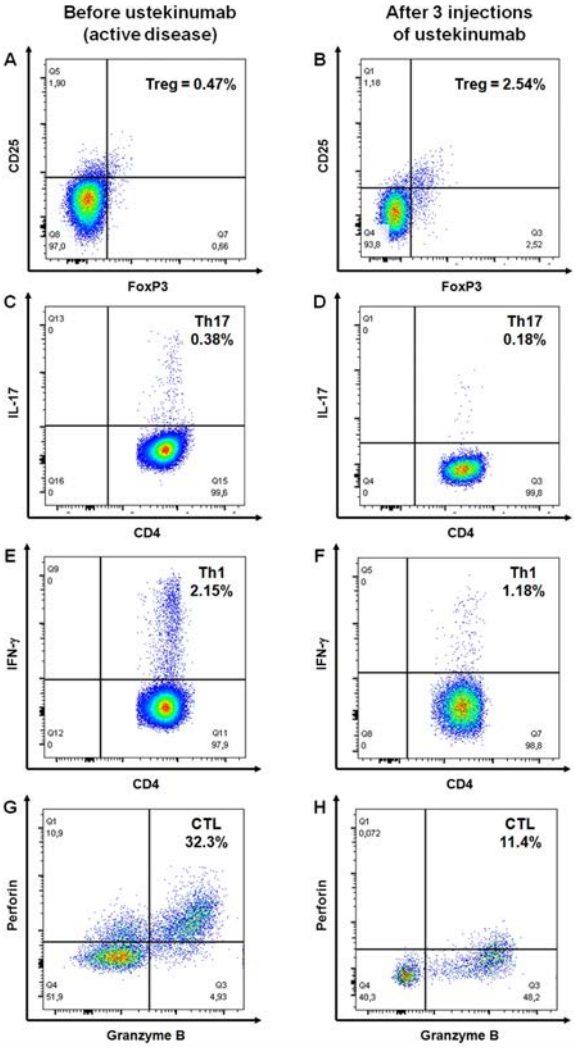


Figure 1 (A, B) flow cytometry analysis of the percentage of Treg (CD4+CD25highFoxP3+) among total CD4+T cells before (A) and after (B) treatment with ustekinumab. Dot plots show the CD25/FoxP3 staining after gating on CD4+T lymphocytes.C, D:flow cytometry analysis of the percentage of Th17 cells (CD3+CD4+IL-17+) among total CD3+CD4+T cells before (C) and after (D) treatment with ustekinumab. (E, F) flow cytometry analysis of the percentage of Th1 cells (CD3+CD4+IFN-γ+) among total CD3+CD4+T cells before (E) and after (F) treatment with ustekinumab. (G, H) flow cytometry analysis of the percentage of cytotoxic T lymphocytes (CTL: CD3+CD8+perforin+granzymeB+) among total CD3+CD8+T cells before (H) and after (H) treatment with ustekinumab. Dot plots show the perforin/granzyme B staining after gating on CD3+CD8+T lymphocytes.CTL, cytotoxic T lymphocyte; IFN, interferon; IL, interleukin.

Three years after the biopsy-proven diagnosis of GCA, a 70-year-old patient started azathioprine (100 mg/day) because of corticodependence. In July 2008, while azathioprine had been stopped, a relapse occurred: weakness, aortitis and C reactive protein (CRP) at 60 mg/L. Therefore, methotrexate was started in association with prednisone. Eighteen months later, the disease remained active (weakness, headache and CRP at 20 mg/L) despite 20 mg/week of methotrexate and 10 mg/day of prednisone. As tocilizumab was contraindicated because of a past history of sigmoiditis, methotrexate was stopped and ustekinumab was started (45 mg at week 0, week 4 and then every 12 weeks) in association with prednisone (10 mg/day). After 4 months of treatment, prednisone was decreased to 8 mg/day and the patient was free of GCA symptoms with a CRP level at 12 mg/L.

Blood samples were obtained before and after 16 weeks of treatment with ustekinumab. Peripheral blood mononuclear cells (PBMCs) were obtained by Ficoll gradient centrifugation and flow cytometry analyses were performed. For intracellular staining of cytokines, PBMCs were stimulated for 4 hours with phorbol-12-myristate-23-acetate and ionomycin in the presence of brefeldin. Data were acquired on an LSRII cytometer and analysed with FlowJo software.

We observed that the proportion of both Th1 and Th17 cells fell by 50% after three injections of ustekinumab (Th17: from 0.38% to 0.18% of total CD4+ cells; Th1: from 2.15% to 1.18% of total CD4+ cells). Consistently with the decrease in Th1 cells, the percentage of circulating cytotoxic T lymphocytes also fell from 32.3% to 11.4% of total CD3+CD8+ T cells. By contrast, Treg increased from 0.47% to 2.54% of total CD4+ T cells (figure 1).

Though our data came from only one patient, they are consistent with the reported efficacy of ustekinumab in GCA.[7] Furthermore, they suggest that ustekinumab, by blocking both IL-12 and IL-23 pathways, could inhibit Th1, Th17 and cytotoxic immune responses and restore the quantitative deficiency of Treg, which is described in GCA.[3] In terms of correction of T-cell homeostasis, the effect of ustekinumab could be more complete than that of tocilizumab, which is effective to treat GCA[8] by targeting the Th17/Treg balance.[9 10]

Maxime Samson,[1,2] Thibault Ghesquière,[2] Sabine Berthier,[1] Bernard Bonnotte[1,2]

[1]Department of Internal Medicine and Clinical Immunology, François Mitterrand Hospital, Dijon University Hospital, Dijon, France
[2]INSERM, UMR1098, University of Bourgogne Franche-Comté, FHU INCREASE, Dijon, France

Correspondence to Pr Bernard Bonnotte, Department of Internal Medicine and Clinical Immunology, François Mitterrand Hospital, Dijon University Hospital, 21000 Dijon, France; bernard.bonnotte@chu-dijon.fr

Acknowledgements The authors thank Marion Ciudad for her help in doing experiments. They thank Anabelle Legrand, Arlette Hamman and Serge Monier from the Plateforme de Cytométrie, Institut Férératif de Recherche 100, Université de Bourgogne. They also thank Philip Bastab22le for his help in writing the manuscript.

Contributors MS and TG did the experiments and collected data. SB included the patient. MS and BB wrote the manuscript.

Competing interests None declared.

Patient consent Obtained

Ethics approval The Institutional Review Board and the Ethics Committee of Dijon University Hospital.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Samson M, Ghesquière T, Berthier S, *et al*. *Ann Rheum Dis* 2018;**77**:e6.

Received 10 April 2017
Accepted 13 April 2017
Published Online First 13 May 2017

► http://dx.doi.org/10.1136/annrheumdis-2017-211669

Ann Rheum Dis 2018;**77**:e6. doi:10.1136/annrheumdis-2017-211622

REFERENCES

1 Proven A, Gabriel SE, Orces C, *et al*. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. *Arthritis Rheum* 2003;49:703–8.
2 Deng J, Ma-Krupa W, Gewirtz AT, *et al*. Toll-like receptors 4 and 5 induce distinct types of vasculitis. *Circ Res* 2009;104:488–95.
3 Samson M, Audia S, Fraszczak J, *et al*. Th1 and Th17 lymphocytes expressing CD161 are implicated in giant cell arteritis and polymyalgia rheumatica pathogenesis. *Arthritis Rheum* 2012;64:3788–98.
4 Corbera-Bellalta M, Planas-Rigol E, Lozano E, *et al*. Blocking interferon γ reduces expression of chemokines CXCL9, CXCL10 and CXCL11 and decreases macrophage infiltration in ex vivo cultured arteries from patients with giant cell arteritis. *Ann Rheum Dis* 2016;75:1177–86.
5 Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. *J Allergy Clin Immunol* 2015;135:626–35.
6 Teng MW, Bowman EP, McElwee JJ, *et al*. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. *Nat Med* 2015;21:719–29.
7 Conway R, O'Neill L, O'Flynn E, *et al*. Ustekinumab for the treatment of refractory giant cell arteritis. *Ann Rheum Dis* 2016;75:1578–9.
8 Villiger PM, Adler S, Kuchen S, *et al*. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2016;387:1921–7.
9 Samson M, Audia S, Janikashvili N, *et al*. Brief report: inhibition of interleukin-6 function corrects Th17/Treg cell imbalance in patients with rheumatoid arthritis. *Arthritis Rheum* 2012;64:2499–503.
10 Miyabe C, Miyabe Y, Strle K, *et al*. An expanded population of pathogenic regulatory T cells in giant cell arteritis is abrogated by IL-6 blockade therapy. *Ann Rheum Dis* 2017;76:898–905.

Response to: ustekinumab inhibits Th1 and Th17 polarisation in a giant-cell arteritis patient by Samson *et al*

We thank Samson *et al* for their interest in our article on ustekinumab in giant-cell arteritis (GCA) and for their comments on our study.[1 2] Our initial pilot study reported promising results with the use of ustekinumab in refractory GCA.[1]

GCA is associated with considerable disease-related and treatment-related morbidity.[3 4] While glucocorticoids remain the cornerstone of treatment, the associated increased rates of adverse events such as fractures, sepsis, hypertension and diabetes mellitus are significant concerns to both physicians and patients.[4] There is a critical unmet need for new treatment options in GCA to minimise the cumulative glucocorticoid burden and thereby reduce the frequency of adverse events.

A number of alternative agents have failed to demonstrate significant efficacy in GCA.[5 6] Recent studies of tocilizumab and abatacept appear to show more promise but require confirmation and may not sufficiently address the underlying pathogenic mechanisms.[7 8] Our current knowledge of GCA pathogenesis implicates dual T-lymphocyte pathways with Th1 and Th17 cells both believed to be important for different aspects of the disease.[9] Therapies targeting one of these pathways alone may lead to symptomatic improvement but unchecked activity in the other. This is of particular concern with agents targeting interleukin (IL)-6, which may have little effect on the Th1 pathway that is believed to be a key player in the ischaemic manifestations in GCA. Ustekinumab is a theoretically attractive treatment option in this setting as it targets both IL-12 and IL-23, which are key cytokines implicated in the Th1 and Th17 pathways, respectively.[9]

Samson *et al* report a case of refractory GCA successfully treated with ustekinumab, which adds to the data from our previous study.[1] Ustekinumab facilitated glucocorticoid tapering and an improvement in C-reactive protein. Samson *et al* used a 45 mg dose of ustekinumab, following the weight-based dosing used in psoriatic arthritis.[2] In our study, all patients were treated with an initial 90 mg dose, although some patients have subsequently successfully reduced the dose to 45 mg when in remission. It is possible that the 90 mg dose would have resulted in an even greater clinical improvement in the patient reported by Samson *et al*.

Samson *et al* report encouraging data on the normalisation of T-cell homeostasis in their patient with ustekinumab.[2] We have recently reported preliminary data on the role of IL-23 in stimulating inflammatory and proliferative pathways in ex vivo models of GCA.[10] The early results from the translational work being performed by our group and by Samson *et al* are suggestive of important roles for IL-12 and IL-23 in GCA. These promising preliminary findings require confirmation in more extensive translational and clinical studies to support the rationale for ustekinumab in the treatment of GCA.

Richard Conway,[1,2] Ursula Fearon,[3] Eamonn S Molloy[1]

[1]Centre for Arthritis and Rheumatic Diseases, St. Vincent's University Hospital, Dublin Academic Medical Centre, Dublin, Ireland
[2]CARD Newman Research Fellow, University College Dublin, Dublin, Ireland
[3]Department of Molecular Rheumatology, School of Medicine, Trinity Biomedical Sciences Institute, Trinity College, Dublin, Ireland

Correspondence to Dr Richard Conway, Centre for Arthritis and Rheumatic Diseases, St Vincent's University Hospital, Dublin Academic Medical Centre, Elm Park, Dublin, Ireland; drrichardconway@gmail.com

Contributors All authors contributed to the manuscript and approved the final version.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

Data sharing statement Data used in this study are held in Bone and Joint Unit, St. Vincent's University Hospital, Dublin, Ireland, under the custody of EM and can be made available on request.

To cite Conway R, Fearon U, Molloy ES. *Ann Rheum Dis* 2018;**77**:e7.

Received 28 April 2017
Accepted 1 May 2017
Published Online First 25 May 2017

► http://dx.doi.org/10.1136/annrheumdis-2017-211622

Ann Rheum Dis 2018;**77**:e7. doi:10.1136/annrheumdis-2017-211669

REFERENCES

1 Conway R, O'Neill L, O'Flynn E, *et al*. Ustekinumab for the treatment of refractory giant cell arteritis. *Ann Rheum Dis* 2016;75:1578–9.
2 Samson M, Ghesquière T, Berthier S, *et al*. Ustekinumab inhibits Th1 and Th17 polarization in a giant cell arteritis patient. *Ann rheum dis* 2018;77:e6.
3 Singh AG, Kermani TA, Crowson CS, *et al*. Visual manifestations in giant cell arteritis: trend over 5 decades in a population-based cohort. *J Rheumatol* 2015;42:309–15.
4 Chandran A, Udayakumar PD, Kermani TA, *et al*. Glucocorticoid usage in giant cell arteritis over six decades (1950 to 2009). *Clin Exp Rheumatol* 2015;33(2 Suppl 89):S-98–102.
5 Seror R, Baron G, Hachulla E, *et al*. Adalimumab for steroid sparing in patients with giant-cell arteritis: results of a multicentre randomised controlled trial. *Ann Rheum Dis* 2014;73:2074–81.
6 Hoffman GS, Cid MC, Rendt-Zagar KE, *et al*. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. *Ann Intern Med* 2007;146:621–30.
7 Villiger PM, Adler S, Kuchen S, *et al*. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *The Lancet* 2016;387:1921–7.
8 Langford CA, Cuthbertson D, Ytterberg SR, *et al*. A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the treatment of giant cell arteritis. *Arthritis Rheumatol* 2017;69:837–45.
9 Deng J, Younge BR, Olshen RA, *et al*. Th17 and Th1 T-cell responses in giant cell arteritis. *Circulation* 2010;121:906–15.
10 Conway R, Creevey K, Trenkmann M, *et al*. Interleukin-23 stimulates inflammatory and proliferative Pathways in Giant Cell Arteritis. *Arthritis Rheumatol.* 2016;68.

ANCA-associated vasculitis: mission incomplete

Over the last decades, introduction of high-dose corticosteroids and immunosuppressive agents and later rituximab into the current algorithms for remission induction and maintenance treatment resulted in a tremendous improvement in the survival of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV). However, in the recent meta-analysis of observational studies, Tan *et al* showed a 2.7-fold increased risk of death in patients with AAV when compared with the general population.[1] Notably, there was a trend towards lower mortality in the most recent compared with the earlier cohorts. In our own study in 242 patients with granulomatosis with polyangiitis, we also found a significant decrease in mortality in the recent years (2004–2012 vs 1970–2003; p=0.04) and a shift towards a higher percentage of cardiovascular events and complications of immunosuppression as the causes of death.[2]

The results of Tan *et al*'s meta-analysis are not surprising and suggest that AAV, particularly if not promptly diagnosed and treated, remains a life-threatening disease and requires proper management. The pitfalls of the current treatment for AAV are well known and include relatively frequent relapses, especially in proteinase-3 (PR3) ANCA-positive patients (up to 50% within 5 years), delayed diagnosis and late initiation of treatment in a proportion of patients, high rate of end-stage renal disease (ESRD), which did not change significantly in the current era, unknown optimal duration of maintenance therapy, burden of immunosuppression (eg, infections and malignancy), and increased risk of cardiovascular and thromboembolic events, which may be related to persistent inflammation and/or corticosteroid treatment.

How can we improve outcomes in patients with AAV? Currently, rituximab seems to be the most promising agent both for remission induction and maintenance treatment. In the RAVE trial, rituximab appeared more effective than cyclophosphamide for relapsing disease and for PR3-ANCA-positive patients with AAV, while in the MAINRITSAN trial prolonged maintenance treatment with low-dose rituximab resulted in a significant reduction in the major relapses rate compared with azathioprine.[3–5] A tailored approach to guide rituximab administration based on serial B lymphocyte and ANCA titre monitoring was studied in the MAINRITSAN 2 (NCT01731561) trial, while the MAINRITSAN 3 (NCT02433522) study will evaluate the need in the longer biological therapy to sustain remission. These trials will advance the understanding of optimal rituximab use for maintenance of remission in patients with AAV. In general, rituximab is regarded as more effective and safe option than cyclophosphamide. However, its advantages over standard immunosuppressives should not be overstated. In the RITUXVAS and RAVE trials, rituximab was equivalent to cyclophosphamide for remission induction of AAV among treatment-naïve patients, while in the MAINRITSAN trial the azathioprine dose was tapered starting at 12 months. The latter schedule of remission maintenance is not well accepted, and 41% of the relapses in the azathioprine group occurred after treatment cessation. Therefore, it can be speculated that the difference in relapse rates between rituximab and azathioprine groups would have been less significant if higher doses of the latter were maintained throughout the entire study. The RITAZAREM trial (NCT01697267) will help answer this question. Unlike cyclophosphamide, rituximab does not induce infertility or haemorrhagic cystitis. However, it can cause serious infections, late-onset neutropenia and hypogammaglobulinaemia. Moreover, in the randomised controlled trials retreatment with rituximab was not associated with a lower rate of adverse events compared with that in the other arms.

In the future, we can expect that targeted agents will continue to expand in the treatment arena. Avacopan (CCX168), an orally administered, selective C5a receptor inhibitor (CCX168), has recently completed phase 2 investigation in patients with AAV in Europe (CLEAR, NCT01363388). In this randomised, placebo-controlled trial, avacopan was effective in replacing high-dose corticosteroids in treating newly diagnosed or relapsing vasculitis.[6] A randomised, double-blind, phase 3 ADVOCATE (NCT02994927) study will evaluate the safety and efficacy of avacopan as an alternative to prednisone in inducing and sustaining remission in patients with AAV treated concomitantly with rituximab or cyclophosphamide/azathioprine. Belimumab, a monoclonal antibody directed against B cell activating factor (BAFF), is currently being investigated in combination with azathioprine for maintenance of remission in AAV in a multicentre, randomised trial (BREVAS; NCT01663623). Belimumab may be probably combined with rituximab, for example, as a sequential therapy. Another ongoing multicentre, double-blind, placebo-controlled phase 3 trial aims to evaluate abatacept, a fusion protein that blocks the costimulatory signal needed for T cell activation, in relapsing non-severe AAV (ABROGATE; NCT02108860).

Renal prognosis is still unfavourable in AAV, as up to 20%–25% of patients reach ESRD within a few years after diagnosis.[7] Adjunct plasma exchange is advocated for patients with a serum creatine level of >500 mmol/L due to rapidly progressive glomerulonephritis in the setting of new or relapsing AAV. It can also be considered for the treatment of severe diffuse alveolar haemorrhage. Short-term results with plasma exchange in patients with ANCA-associated glomerulonephritis were encouraging, but the long-term benefits remain unclear.

Patients with AAV have an increased risk of cardiovascular events that may be determined by highly prevalent traditional risk factors, such as hypertension, dyslipidaemia and type 2 diabetes, vasculitis itself and/or atherogenic effects of corticosteroids. Therefore, in addition to vigorous risk factors, modification of steroid-sparing strategies may confer protective effects against atherosclerotic cardiovascular disease. However, a higher relapse rate may be a price we pay for a lower dose or too rapid tapering of prednisone. Several trials, that is, PEXIVAS, LoVAS and TAPIR, will add evidence regarding the efficacy of different corticosteroid regimens for remission induction and maintenance.

The recent EULAR/ERA-EDTA recommendations for the management of AAV did not address the risk of venous thromboembolic events[8] that occur in up to 10% of patients within the first few months after diagnosis or relapse of vasculitis.[9] Risk/benefit ratio of anticoagulation in patients with AAV is not established. Therefore, routine administration of oral anticoagulants cannot be recommended. In a large cohort of patients with AAV (n=377), we were unable to establish sufficiently strong predictors of venous thromboembolic events, except a short time after diagnosis, that would justify thromboprophylaxis with oral anticoagulants. Thus, it is currently unknown how to use this double-edged sword in real-life clinical practice.

In summary, observational studies have inherent limitations in terms of their susceptibility to bias and confounding. Risk of bias is particularly high in patients with AAV since they constitute a heterogeneous group and have variable course and response to treatment (eg, eosinophilic granulomatosis with

polyangiitis (EGPA) vs granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), renal vs non-renal vasculitis, localised vs generalised GPA), not to mention the ongoing discussion regarding classification of AAV (ANCA specificity based or a nosological scheme, the possible need to revise current definition for EGPA). However, observational studies give an idea about the prevalence and prognosis of the disease and reflect daily clinical practice more closely than randomised controlled trials. Tan *et al*'s meta-analysis suggests that there is room for further improvement in management of patients with AAV with the ultimate goal to reduce mortality and disability while avoiding both undertreatment and overtreatment. There is a need for longitudinal studies to evaluate mortality benefits of modern therapies and trends in the leading causes of death of patients with AAV. These data may facilitate decision making and support new preventive strategies.

Sergey V Moiseev,[1] Pavel I Novikov,[1] Ilya Smitienko[2]

[1]Clinic of Nephrology, Internal and Occupational Diseases, Sechenov First Moscow State Medical University, Moscow, Russian Federation
[2]Medical Center "K + 31", Moscow, Russian Federation

Correspondence to Professor Sergey V Moiseev, Clinic of Nephrology, Internal and Occupational Diseases, Sechenov First Moscow State Medical University, Rossolimo 11/5, Moscow 119435, Russian Federation; clinpharm@mtu-net.ru

Contributors All authors contributed to review of the manuscript.

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Moiseev SV, Novikov PI, Smitienko I. *Ann Rheum Dis* 2018;**77**:e8.

Received 10 May 2017
Accepted 12 May 2017
Published Online First 12 June 2017

► http://dx.doi.org/10.1136/annrheumdis-2017-211792

Ann Rheum Dis 2018;**77**:e8. doi:10.1136/annrheumdis-2017-211773

REFERENCES

1 Tan JA, Dehghan N, Chen W, *et al*. Mortality in ANCA-associated vasculitis: a meta-analysis of observational studies. *Ann Rheum Dis* 2017;76:1566–74.
2 Novikov PI, Moiseev SV, Kuznetsova EI, *et al*. Changing patterns of clinical severity and risk of mortality in granulomatosis with polyangiitis over four decades: the Russian experience. *Rheumatol Int* 2015;35:891–8.
3 Stone JH, Merkel PA, Spiera R, *et al*. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010;363:221–32.
4 Miloslavsky EM, Specks U, Merkel PA, *et al*. Clinical outcomes of remission induction therapy for severe antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2013;65:2441–9.
5 Guillevin L, Pagnoux C, Karras A, *et al*; French Vasculitis Study Group. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 2014;371:1771–80.
6 Jayne DR, Bruchfeld AN, Harper L, *et al*. Randomized Trial of C5a receptor inhibitor avacopan in ANCA-Associated vasculitis. *J Am Soc Nephrol* 2017:ASN.2016111179.
7 Moiseev S, Novikov P, Jayne D, *et al*. End-stage renal disease in ANCA-associated vasculitis. *Nephrol Dial Transplant* 2017;32:248–53.
8 Yates M, Watts RA, Bajema IM, *et al*. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis* 2016;75:1583–94.
9 Novikov P, Makarov E, Moiseev S, *et al*. Venous thromboembolic events in systemic vasculitis. *Ann Rheum Dis* 2015;74:e27.

Response to: 'Mortality in ANCA-associated vasculitis: mission incomplete' by Moiseev *et al*

We thank Professor Moiseev and colleagues for their comments on our article.[1] We acknowledge the limitations of including observational studies in our meta-analysis. We also agree that observational studies often suffer from confounding and selection biases, limiting the comparability between studies.[2] This was also reflected by the relatively high between-studies heterogeneity score (I^2=84.4%, 95% CI 72.6 to 96.3), which was not unexpected. As such, we focused considerably on examining the source of variability in results across the studies and not just on the statistical combination of data from the meta-analysis. This would provide important insights into the biases and confounding factors prevalent in observational studies. Furthermore, we have also demonstrated that it can generate questions for hypothesis testing. When a meta-analysis of observational studies is done well in accordance to recommendations,[3] it has some advantages over randomised controlled trials (RCTs) in the reporting of risk factor associations and disease/treatment outcomes in the community. We should mention that RCTs of therapeutic interventions are designed to test efficacy and therefore are not designed to assess mortality as the primary outcome. In this regard, longitudinal studies in a contemporary general population setting might be better served in answering questions about the mortality benefits of modern therapy in AAV patients. We are confident that the ongoing clinical trials in patients with ANCA associated vasculitis (AAV) will continue to examine and, hopefully, improve long-term survival in these patients.

Juan Antonio Avina-Zubieta,[1,2] Natasha Dehghan,[2] Ju Ann Tan[1,3]

[1]Arthritis Research Canada, Vancouver, British Columbia, Canada
[2]Division of Rheumatology, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada
[3]Department of Rheumatology, Western Health, Footscray, Victoria, Australia

Correspondence to Dr Juan Antonio Avina-Zubieta, Arthritis Research Canada, Vancouver, British Columbia, V5Z 1L7, Canada; azubieta@arthritisresearch.ca

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Avina-Zubieta JA, Dehghan N, Tan JA. *Ann Rheum Dis* 2018;**77**:e9.

Received 9 June 2017
Accepted 12 June 2017
Published Online First 14 July 2017

► http://dx.doi.org/10.1136/annrheumdis-2017-211773

Ann Rheum Dis 2018;**77**:e9. doi:10.1136/annrheumdis-2017-211792

REFERENCES

1 Moiseev SV, Novikov PI, Smitienko I. ANCA-associated vasculitis: mission incomplete. *Ann Rheum Dis* 2018;77:e8.
2 Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. *BMJ* 1998;316:140–4.
3 Stroup DF, Berlin JA, Morton SC, *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008–12.

Comment on CONCEPT by Reginster *et al*: are the authors' interpretations supported by the data analysis?

I read with great interest the ChONdroitin versus CElecoxib versus Placebo Trial (CONCEPT) by Reginster *et al*.[1] I would like to raise some worthwhile issues that need to be clarified.

The authors concluded that 800 mg/day pharmaceutical-grade chondroitin sulfate (CS) is similar to celecoxib in improving pain and function after 6 months in patients with symptomatic knee osteoarthritis (OA).[1] However, the interpretation of similarity between these two active treatments was not based on the analysis of the data. Because, the authors did not assess whether these treatments are similar by equivalence analysis. Rather, the authors assessed the superiority between these two active treatments by aiming to detect a difference in intention-to-treat (ITT) populations—although the study might not be powered to be able to detect differences between these two active treatments (type 2 error), since sample size is calculated to show superiority of CS over placebo; and they failed to show a difference between CS and celecoxib. According to the Consolidated Standards of Reporting Trials 2010 statement on reporting of non-inferiority and equivalence randomised trials, 'Failure to show a difference does not mean they are equivalent. By contrast, equivalence trials aim to determine whether one (typically new) intervention is therapeutically similar to another (usually an existing) treatment. A noninferiority trial seeks to determine whether a new treatment is not worse than a reference treatment by more than an acceptable amount', and similarity conclusion should be drawn by the equivalence analysis.[2] In superiority analysis, ITT analysis is widely recommended as the preferred primary analysis strategy;[3 4] but in non-inferiority or equivalence analysis, ITT and per protocol (PP) analysis have equal importance and for a robust interpretation both of the analyses should be performed[4] based on a prestated margin of non-inferiority ($-\Delta$) or equivalence ($-\Delta$ and $+\Delta$).[2 4] However, the authors did not perform PP analysis and more importantly they did not define equivalence margin ($-\Delta$ and $+\Delta$); and without them, the interpretation/conclusion of similarity is not possible to be drawn.

In CONCEPT, no missing values replacement was performed for the analysis. This approach might be satisfactory with a small amount of missing data,[5] and a few missing outcomes will not cause a problem.[3] However, in CONCEPT, the dropout rate was higher (99/604=16.3%, 505 completers, at 6 months) than expected in the sample size calculation (90/600=15%, 510 completers). Therefore, this approach ignoring missing data reduced the statistical power by decreasing the sample size and might lead to serious biases.[3 5] In such cases with high missing data due to dropout, sensitivity analyses using multiple imputation under various informative missingness scenarios are recommended to preserve the statistical power.[5 6] In CONCEPT, that recommended approach should have been conducted to mitigate the potential biases associated with a relatively high dropout rate.

In CONCEPT, more than one primary variable was used but type 1 error was not controlled. The European Medicines Agency (EMA) guideline on statistical principles for clinical trials recommends that in studies that use multiple primary variables, a method of controlling type 1 error should be performed because of the potential for multiplicity problems; except when the aim of the study is to show effects on all of the multiple primary variables, the adjustment of the type 1 error is not needed.[7] Since, in CONCEPT, the primary variables were interpreted separately, particularly at 3 months where CS demonstrated a statistically greater reduction in Lequesne Index but not in pain than placebo, a method of controlling the false positive rate (type 1 error) should have been performed, as recommended by the EMA guidelines.[7]

For the studies of symptomatic response of symptom-modifying drugs, a patient population with Kellgren-Lawrence (K-L) grade ≥2 might be more appropriate, according to the Osteoarthritis Research Society International (OARSI) recommendations;[8 9] and this patient population group constitutes the study sample of the recent high-quality studies.[10–13] However, the CONCEPT included K-L grades 2–3 and K-L grade 1. The inclusion of K-L grade 1 is possible but induces heterogeneity in the population. In the situation of heterogeneity, the sample size should ideally be increased to permit stratified analyses of the subpopulation.[8] However, in CONCEPT, the sample size was not adjusted according to the radiographic grade to permit stratified analyses and K-L grade 1 combined into K-L grades 2–3; hence positive results for a responsive subpopulation might be masked because of heterogeneity, as explained in OARSI recommendations.[8] This important issue should be considered when interpreting the results of CONCEPT.

The authors mentioned that a group of European academic scientists and regulators suggest that at least a 5 mm difference on a 100 mm visual analogue scale (VAS) for pain intensity between the active drug and placebo constitutes a clinically relevant threshold for symptomatic slow-acting drugs for OA (SYSADOAs)[14] ; and the authors noted that in CONCEPT, the difference in reduction of pain intensity among CS and placebo is 8.2 mm after 6 months. Indeed, according to that guideline the difference should be at least 5 mm, but it should be shown at repeated time points to be able to consider a benefit of SYSADOA over placebo as clinically relevant.[14] In CONCEPT, the difference in pain did not reach 5 mm after 1–3 months, and no available data exist beyond 6 months; therefore on the basis of CONCEPT data, it is not possible to consider benefits of CS as clinically relevant.

In conclusion, I believe that the concerns raised above should be taken into consideration when interpreting the authors' results and conclusions. Also, I strongly believe that the interpretation/conclusion of similarity between CS and celecoxib was not supported by the data analysis.

Sinan Kardeş

Department of Medical Ecology and Hydroclimatology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

Correspondence to Dr Sinan Kardeş, Tıbbi Ekoloji ve Hidroklimatoloji A.B.D. Istanbul Tıp Fakültesi Fatih, Çapa, Istanbul, Turkey 34093; snnkrds@gmail.com

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Kardeş S. *Ann Rheum Dis* 2018;**77**:e10.

Received 24 July 2017
Accepted 25 July 2017
Published Online First 10 August 2017

► http://dx.doi.org/10.1136 annrheumdis-2017-212165

Ann Rheum Dis 2018;**77**:e10. doi:10.1136/annrheumdis-2017-212115

REFERENCES

1 Reginster JY, Dudler J, Blicharski T, *et al*. Pharmaceutical-grade chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: The Chondroitin Versus Celecoxib Versus Placebo Trial (CONCEPT). *Ann Rheum Dis* 2017;76:1537–43.
2 Piaggio G, Elbourne DR, Pocock SJ, *et al*. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012;308:2594–604.
3 Moher D, Hopewell S, Schulz KF, *et al*. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c869.
4 Committee for Proprietary Medicinal Products (CPMP). *Points to consider on switching between superiority and non-inferiority*. London: European Medicines Agency (EMA), 2000.
5 Olsen IC, Kvien TK, Uhlig T. Consequences of handling missing data for treatment response in osteoarthritis: a simulation study. *Osteoarthritis Cartilage* 2012;20:822–8.
6 Liao JM, Stack CB. Annals understanding clinical research: implications of missing sata due to dropout. *Ann Intern Med* 2017;166:596–8.
7 ICH Topic E 9 Statistical Principles for Clinical Trials. *Note for guidance on statistical principles for clinical trials*. London: European Medicines Agency (EMA), 1998.
8 McAlindon TE, Driban JB, Henrotin Y, *et al*. OARSI clinical trials recommendations: design, conduct, and reporting of clinical trials for knee osteoarthritis. *Osteoarthritis Cartilage* 2015;23:747–60.
9 Altman R, Brandt K, Hochberg M, *et al*. Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the osteoarthritis research society. Results from a workshop. *Osteoarthritis Cartilage* 1996;4:217–43.
10 Clegg DO, Reda DJ, Harris CL, *et al*. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006;354:795–808.
11 Herrero-Beaumont G, Ivorra JA, Del Carmen Trabado M, *et al*. Glucosamine sulfate in the treatment of knee osteoarthritis symptoms: a randomized, double-blind, placebo-controlled study using acetaminophen as a side comparator. *Arthritis Rheum* 2007;56:555–67.
12 Hochberg MC, Martel-Pelletier J, Monfort J, *et al*. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. *Ann Rheum Dis* 2016;75:37–44.
13 Roman-Blas JA, Castañeda S, Sánchez-Pernaute O, *et al*. Combined treatment with chondroitin sulfate and glucosamine sulfate shows no superiority over placebo for reduction of joint pain and functional impairment in patients with knee osteoarthritis: a six-month multicenter, randomized, double-blind, placebo-controlled clinical trial. *Arthritis Rheumatol* 2017;69:77–85.
14 Reginster JY, Reiter-Niesert S, Bruyère O, *et al*. Recommendations for an update of the 2010 European regulatory guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis and reflections about related clinically relevant outcomes: expert consensus statement. *Osteoarthritis Cartilage* 2015;23:2086–93.

CONCEPT provides robust evidence that chondroitin sulfate is superior to placebo and similar to celecoxib in the symptomatic management of osteoarthritis

We are very grateful to our distinguished colleague for his constructive comments.[1] However it seems that some keypoints of our study were grossly misunderstood.[2] As clearly stated, the objective of the CONCEPT study was to confirm that chondroitin sulfate (CS) is superior to placebo (PLB) in the symptomatic treatment of osteoarthritis, with the addition of a Celebrex (CLB) arm, as requested by the European Medicines Agency, to provide an external validation and to better assess the relevance of the difference in pain relief observed between the CS and PLB arms. There was no intent to demonstrate a non-inferiority of CS versus Celebrex. In such a case, a non-inferiority margin for the comparison would be mentioned in the protocol, and the power calculation would be substantially different. The use of the word similar in describing Visual Analogue Scale (VAS) and Lequesne scoring outcomes for CS compared with CLB is subsequently fully appropriate and is consistent with the general meaning of the word, which is devoid of any statistical connotation.

Interestingly, please note that 95% CIs were calculated for CS versus CLB (clinical study report, data on file), and the lower or upper boundaries of the CI are well within what would have been considered as a conservative prestudy non-inferiority margin, in case a non-inferiority trial was considered.

The differences in VAS pain reduction after 6 months between CS and CLB are summarised in table 1.

The statistical analysis of the primary endpoints was carried out using a linear mixed model with patient as random effect and centre, treatment group, time point, interaction between treatment groups and time points as categorical covariates.

We acknowledge that additional sensitivity analyses can be considered. Such analyses were, actually, performed (data on file), but did not show relevant differences. Therefore, for the sake of concision, these supplementary data were not included in the article. We also used an analysis of covariance (ANCOVA) model using a baseline observation carried forward (BOCF) method, in addition to an ANCOVA model using last observation carried forward (LOCF) and an ANCOVA model using a combination of LOCF and BOCF methods to replace missing values, taking into account the reason for early withdrawals and eventually a multivariate ANCOVA including age, gender and body mass index as additional covariates. Furthermore, all the analyses were also conducted in the per-protocol population and yielded identical results compared with those obtained in the intention-to-treat population, published in our article.

Table 1 Differences in VAS pain reduction after 6 months between CS and CLB

Model	Difference	95% CI
Linear mixed model	1.864	−2.933 to 6.660
ANCOVA—BOCF	−0.274	−5.004 to 4.456
ANCOVA—LOCF	0.360	−4.202 to 4.922
ANCOVA—BOCF+LOCF	0.064	−4.606 to 4.734
Multivariate ANCOVA	−0.153	−4.849 to 4.543

ANCOVA, analysis of covariance; BOCF, baseline observation carried forward; CLB, Celebrex; CS, chondroitin sulfate; LOCF, last observation carried forward; VAS, Visual Analogue Scale.

Table 2 Visual Analogue Scale pain reduction

Comparison	Difference mean (SE)*	p Value
CS—placebo—day 30	0.331 (2.007)	0.869
Celebrex—placebo—day 30	2.831 (2.007)	0.159
CS—placebo—day 91	1.820 (2.299)	0.429
Celebrex—placebo—day 91	2.861 (2.293)	0.213
CS—placebo—day 182	8.192 (2.435)	0.001
Celebrex—placebo—day 182	6.328 (2.405)	0.009

* Estimated mean and SE from a mixed-model analysis.
CS, chondroitin sulfate.

Table 3 Lequesne Index reduction

Comparison	Difference mean (SE)*	p Value
CS—placebo—day 30	0.125 (0.342)	0.714
Celebrex—placebo—day 30	0.686 (0.342)	0.045
CS—placebo—day 91	0.725 (0.370)	0.050
Celebrex—placebo—day 91	0.820 (0.369)	0.027
CS—placebo—day 182	0.963 (0.423)	0.023
Celebrex—placebo—day 182	1.022 (0.419)	0.015

*Estimated mean and SE from a mixed-model analysis.
CS, chondroitin sulfate.

The primary outcome measures for this study were the changes in VAS pain and in Lequesne Index (LI) observed from day 1 to day 182. As expected from the previous literature, both co-primary endpoints were significantly reduced by each treatment. No adjustment of type 1 error was performed in accordance to the study protocol, which requires the primary endpoint analysis to be based on the demonstration of a difference between CS and PLB reaching the level of statistical difference of $p<0.05$ for both VAS pain and LI at day 182 only.

Patients with Kellgren-Lawrence (KL) scores from 1 to 4 (grades 2–3 corresponding to 75% of the study population) were enrolled in the study, which is representative of the patient population that will ultimately be treated with long-term CS. Whether CS is more or less effective in one or another KL grade is beyond the scope of the present trial.

Reduction in VAS pain scores for patients with both CS and CLB was numerically higher compared with PLB as soon as 1 month post-inclusion, reaching statistical significance after 6 months. Decrease in LI reached significance at 1, 3 and 6 months for CLB versus PLB and at 3 and 6 months for the CS versus PLB comparison, an observation which is consistent both for CLB (a non-steroidal anti-inflammatory drug with a fast onset of action) and for CS (a member of the class of slow-acting drugs in osteoarthritis). We provide here the detailed results of these comparisonsin tables 2 and 3.

We hope that these comments will contribute to a better understanding of the role of pharmaceutical-grade CS as a background treatment of knee osteoarthritis.[3]

Jean-Yves L Reginster, on behalf of CONCEPT Investigation Group

Department of Public Health, Epidemiology and Health Economics, Liege State University, Liege, Liege, Belgium

Correspondence to Professor Jean-Yves L Reginster, Department of Public Health, Epidemiology and Health Economics, Liège State University, Liège CHU B23 , Belgium; jyreginster@ulg.ac.be

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Reginster J-YL, on behalf of CONCEPT Investigation Group. *Ann Rheum Dis* 2018;**77**:e11.

Received 6 September 2017
Revised 12 September 2017
Accepted 15 September 2017
Published Online First 22 September 2017

► http://dx.doi.org/10.1136/annrheumdis-2017-212115

Ann Rheum Dis 2018;**77**:e11. doi:10.1136/annrheumdis-2017-212165

REFERENCES

1 Kardeş S. Comment on CONCEPT by Reginster et al: are the authors' interpretations supported by the data analysis? *Ann Rheum Dis* 2018;77:e10.
2 Reginster JY, Dudler J, Blicharski T, *et al*. Pharmaceutical-grade chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the ChONdroitin versus CElecoxib versus Placebo Trial (CONCEPT). *Ann Rheum Dis* 2017;76:1537–43.
3 Bruyère O, Cooper C, Pelletier JP, *et al*. A consensus statement on the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for the management of knee osteoarthritis—from evidence-based medicine to the real-life setting. *Semin Arthritis Rheum* 2016;45:S3–S11.