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://ard.bmj.com/pages/authors/).

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

Contact Details

Editorial Office
Annals of the Rheumatic Diseases
BMJ Journals, BMA House, Tavistock Square
London WCIH 9JR,UK
E: **ard@bmj.com**

Production Editor
Teresa Jobson
E: **production.ard@bmj.com**

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

Customer support
For general queries and support with existing and new subscriptions:
W: **support.bmj.com**
T: **+44 (0)20 7111 1105**
E: **support@bmj.com**

Self-archiving and permissions
W: **bmj.com/company/products-services/rights-and-licensing/**
E: **bmj.permissions@bmj.com**

Advertising
W: **bmj.com/company/for-advertisers-and-sponsor/**

Display Advertising ROW
Sophie Fitzsimmons
T: **+44 (0)20 3655 5612**
E: **sfitzsimmons@bmj.com**

Online Advertising ROW
Marc Clifford
T: **+44 (0) 20 3655 5610**
E: **mclifford@bmj.com**

Display & Online Advertising Americas
Jim Cunningham
T: **+1 201 767 4170**
E: **jcunningham@cunnasso.com**

Reprints

Author Reprints
BMJ Reprints Team
E: **admin.reprints@bmj.com**

Commercial Reprints ROW
Nadia Gurney-Randall
M: **+44 07866 262344**
E: **ngurneyrandall@bmj.com**

Commercial Reprints Americas
Ray Thibodeau
T: **+1 267 895 1758**
M: **+1 215 933 8484**
E: **ray.thibodeau@contentednet.com**

For all other journal contacts
ard.bmj.com/contact-us

Subscription Information

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

Institutional Rates 2021

Print
£1,121

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 2021

Print (includes online access at no additional cost)
£431

Online only
£241

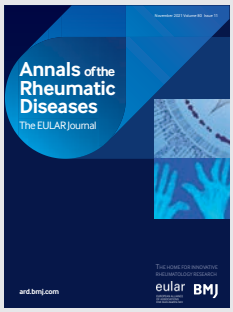
EULAR congress delegates
Delegates receive a Continuous Professional Development package that includes a 12 month complimentary subscription to *ARD* in print and/or online

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

For more information on subscription rates or to subscribe online please visit ard/bmj.com/pages/contact-us/

ARD
The Eular Journal
Impact Factor: 19.103



Editorial office
Annals of the Rheumatic Diseases
BMJ Publishing Group Ltd
BMA House
Tavistock Square
London WCIH 9JR,UK
T: **+44 (0)20 3655 5889**
E: **ard@bmj.com**
Twitter: **@ARD_BMJ**
ISSN: 0003-4967 (print)
ISSN: 1468-2060 (online)

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 0003-4967 (USPS 2152) is published monthly by BMJ Publishing Group Ltd, BMA House, Tavistock Square, WC1H 9JR London. Airfreight and mailing in the USA by agent named World Container Inc, 150-15, 183rd Street, Jamaica, NY 11413, USA. Periodicals postage paid at Brooklyn, NY 11256. US Postmaster: Send address changes to Annals of the Rheumatic Diseases, World Container Inc, 150-15, 183rd Street, Jamaica, NY 11413, USA. Subscription records are maintained at BMA House, Tavistock Square, WC1H 9JR London. Air Business Ltd is acting as our mailing agent.

MORE CONTENTS ►

What is the optimal target for a T2T approach in axial spondyloarthritis?

Joachim Sieper , Denis Poddubnyy

An international expert group had formulated and recently updated a set of recommendations for treatment targets (treat to target—T2T) in axial spondyloarthritis (axSpA).[1] According to these recommendations, the treatment target should be clinical remission/inactive disease defined as the absence of clinical and laboratory evidence of significant disease activity, which is currently best defined by reaching an Ankylosing Disease Activity Score (ASDAS) <1.3, termed ASDAS inactive disease.[2] In some mostly older studies, information is only available for another remission outcome, Assessment of Spondyloarthritis International Society (ASAS) partial remission.[3] Only if it is not possible to achieve remission a low disease activity, which is defined as ASDAS <2.1, can be taken as an alternative target. Indeed, in observational axSpA cohorts, patients with an ASDAS <1.3 showed less spinal radiographic progression compared with patients with a higher ASDAS[4 5] and patients treated with tumour necrosis factor (TNF) blockers also showed less radiographic progression if the ASDAS was reduced to values <1.3.[6] In addition, disease activity should be measured and treatment should be adjusted frequently (tight control) in order to reach an optimal control of disease activity.

On this background, a clinical trial investigating the concept of T2T in axSpA (1) has to define a treatment target to be reached, (2) has to define the frequency of the control measurements (tight control), (3) has to outline the treatment escalation in case the target is not reached and, finally, (4) an adequate control group has to be selected. To a further extent, it is desirable to demonstrate short-term and also long-term benefits of the T2T approach including inhibition of structural damage progression. Potential benefits should be carefully weighed against potential risks, for example, risks associated with an intensified treatment in the T2T arm.

The study on T2T in axSpA published in this issue of the journal (TICOSPA) was therefore urgently needed and the results eagerly awaited for.[7] For the treatment target, the authors chose low disease activity (ASDAS<2.1). Currently, it is not known if targeting low disease activity (that implies no treatment escalation if the ASDAS <2.1 but still >1.3 is reached) has disadvantages as compared with targeting inactive disease (ASDAS<1.3). In the opinion of the authors of this editorial, this question has to be explored in future trials using the T2T approach. The possibility to achieve ASDAS inactive disease is confirmed by data showing that in patients with axial spondyloarthritis—covering both patients with non-radiographic axSpA and radiographic (r) axSpA, also termed ankylosing spondylitis—who are selected based on shorter disease duration and the presence of objective signs of inflammation, such as an elevated C reactive protein (CRP) or active bony inflammation on MRI, inactive disease (ASDAS<1.3) can be reached consistently in between 45% and 50% of patients treated with a TNF blocker.[8–11] Such a proportion of good responders is clearly lower in patients with axSpA not selected for such variables,[12] as was done also in the TICOSPA study. Indeed, ASDAS inactive disease was reached in 26.4% of patients in the T2T arm while 59.7% reached ASDAS low disease activity.

Once remission is achieved, the next step is to maintain this disease state.[1] In a recent study, patients with axSpA with a disease duration <5 years were treated with the TNF blocker certolizumab pegol, and in those patients reaching remission (ASDAS<1.3 at weeks 32/36 and 48), the possibility of tapering treatment was investigated.[11] Sustained low disease activity throughout week 96, which was chosen as the primary endpoint here, was reached by 84% (87/104) versus 73.0% (77/105) versus 19% (20/104) of patients continuing the full dose of certolizumab, versus half of the dose versus placebo, respectively. The results were not very much lower if analysed for ASDAS inactive disease: 72% (75/104), 55% (58/105) and 13% (14/104) of the second phase randomised patients, respectively, arguing that ASDAS inactive disease could also have been chosen as a primary endpoint without losing too many patients in such a study.

Escalation steps are quite limited in the treatment of axSpA and, as the first pre-biologic step, are restricted to non-steroidal anti-inflammatory drugs (NSAIDs). This is different, for example, to psoriatic arthritis. In another T2T study, the Tight Control in Psoriatic Arthritis (TICOPA) study, an escalation with a conventional synthetic disease-modifying anti-rheumatic drug (DMARD) such as methotrexate and others was possible and was used.[13] The potential of NSAIDs in the treatment as the first step is often neglected in axSpA[14] and the ASAS NSAIDs intake index[15] was indeed rather low in TICOSPA with a score between 30 and 40 at the time of enrolment and was not further increased in the T2T arm up to week 12, and went even further down during the study year in both arms. A question whether a combination of NSAID with a TNF-blocking agent is better than a TNF-blocking agent alone still awaits an answer in a prospective trial.

In a previous study comparing infliximab plus naproxen versus naproxen alone in early axSpA, we could show that ASDAS inactive disease was reached by 19.6% (and ASAS partial remission in 35.3%) of patients treated with naproxen alone and in 51.4% of patients treated with a combination of naproxen plus infliximab.[9] Unfortunately, in this study an infliximab alone arm was not included. Thus, although NSAIDs and infliximab treatment both proved to be quite effective in this study, it remained unclear whether a combination therapy of a TNF blocker plus NSAID is better than TNF-blocker therapy alone. Some information on this question will become available rather soon: in a currently ongoing study (CONSUL) in patients with AS, good responders to TNF-blocker treatment (golimumab) in the first 3 months are then randomised for 2 years for a treatment with the TNF blocker alone or TNF blocker plus celecoxib 400 mg per day.[16] Although the primary endpoint in this study will be radiographic progression, we will also get important information on whether a combination of TNF blocker with NSAIDs, compared with TNF blocker alone, has an effect on disease activity.

The first escalation step after NSAIDs treatment would be TNF blockers and it has also become possible in the last

Department of Gastroenterology, Infectious Diseases and Rheumatology, Charité Universitätsmedizin Berlin, Berlin, Germany

Correspondence to Professor Joachim Sieper, Medical Department I, Rheumatology, Charite Universitatsmedizin Berlin, Berlin 12200, Germany; joachim.sieper@charite.de

years to further switch to an interleukin (IL)−17 inhibitor[17] or even to start with an IL-17 inhibitor just after NSAIDs. In TICOSPA, only two patients were treated with the IL-17 inhibitor secukinumab after anti-TNF failure; thus, further studies are needed to address the optimal strategy after failure of the first-line DMARD. Most recently, the first Janus kinase (JAK) inhibitor upadacitinib (a JAK-1 inhibitor) has been approved for the indication of ankylosing spondylitis[18] and another trial with this drug is ongoing for nr-axSpA, which will enlarge the treatment armamentarium for axSpA further. However, although in the current ASAS/EULAR treatment recommendations it is suggested to start with a TNF blocker as the first biologic[17]—only because we have much longer experience with this class of drug not because they are more effective—we do not have data helping us to decide with which biologic or targeted synthetic DMARD to start and whether specific patients would be better candidates for one or the other DMARD. Similarly, we do not know the optimal sequence of switching between the biologic and whether a combination of biologics (or a biologic and a targeted synthetic DMARD) might be an option in patients who have failed one or two biologics.[19] Furthermore, it has to be further explored if drugs with a direct inhibitory effect on CRP production (that could be the case for JAK inhibitors' mediated IL-6 inhibition) might be associated with a higher probability of ASDAS inactive disease/low disease activity achievement just because of CRP effect and not because of clinical efficacy. For an optimal T2T design, such information would be mandatory.

A normal treatment control group for a T2T study would be standard care, which was also the case in the current TICOSPA study. However, the European centres selected for the current study were—for both the T2T arm and for the standard care arm—interested or even specialised in SpA making it likely that the treating (standard care) physicians followed the ASAS/EULAR recommendations for the treatment of axSpA[17] which are similar to the one applied in the T2T arm. Furthermore, patients and investigators were not blinded for the treatment arms, which might have induced a larger placebo response in the T2T arm.

However, as an advantage, such a study design permits to apply the results immediately to daily clinical practice because every physician can use such a T2T approach for their patients. The results in the T2T arm were indeed numerically (not reaching statistical significance) better for many variables suggesting that using a pre-specified strategy based on treatment intensification until achieving a target, in this case an ASDAS of <2.1, might be superior to standard care. For example, an improvement of the ASAS health index[20] by 30% (the primary endpoint) was reached by 47.3% in the T2T arm versus 36.1% in the control arm and low disease activity was reached in 59.7% versus 50.8%, respectively. The results would have even been probably more in favour of the T2T arm if rheumatologists not specialised in SpA had been selected for the study. Interestingly, also a cost-utility analysis favoured the T2T arm. In the TICOSPA study, the overall number of adverse events was with 33 versus 22 higher in the T2T arm as compared with the usual care arm, mostly driven by allergic reactions, a result which this should be part of the risk–benefit assessment.

The results of the TICOSPA study might even be of more relevance with regard to the axSpA treatment recommendations by ACR/SAA/SPARTAN[21] because disease activity scores are not part of these recommendations and active disease is defined by the severity of patient's symptoms without further specification, thus being more similar to the control arm in TICOSPA.

However, if a T2T study in axSpA wants to address the questions whether remission can be reached, how remission can be reached and whether reaching remission (and maintaining remission) by a T2T approach is superior to usual care, and to achievement of low disease activity instead of remission, on the long term, a prospective interventional study (rather studies, since it would not be possible to address all questions in just one study) would be necessary. Especially for the treatment escalation step after NSAIDs failure, more information should be available from (yet to be planned) trials about the selection of the first biologic according to the patients' characteristics, about the switch of biologics and about the potential of combinations of drugs. At the moment, we only have very limited information about specific treatments on the group level and even this only by indirect comparisons.

Handling editor Josef S Smolen

Contributors Both authors contributed to the design and to the writing of this article (editorial).

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests JS: consulting fees from AbbVie; UCB speaker fees from AbbVie, Janssen, Novartis and Merck. DP: research support from AbbVie, Eli Lilly, MSD, Novartis and Pfizer; consulting fees from AbbVie, Biocad, Gilead, GlaxoSmithKline, Eli Lilly, MSD, Novartis, Pfizer and Samsung Bioepis; UCB speaker fees from AbbVie, Bristol-Myers Squibb, Eli Lilly, MSD, Novartis, Pfizer and UCB.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

To cite Sieper J, Poddubnyy D. *Ann Rheum Dis* 2021;**80**:1367–1369.

Received 1 June 2021
Accepted 9 June 2021
Published Online First 18 June 2021

Linked

► http://dx.doi.org/10.1136/annrheumdis-2020-219585

Ann Rheum Dis 2021;**80**:1367–1369. doi:10.1136/annrheumdis-2021-220603

ORCID iDs
Joachim Sieper http://orcid.org/0000-0003-0285-9890
Denis Poddubnyy http://orcid.org/0000-0002-4537-6015

REFERENCES

1 Smolen JS, Schöls M, Braun J, *et al*. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann Rheum Dis* 2018;77:3–17.
2 Machado PM, Landewe R, Heijde DV, Assessment of SpondyloArthritis international Society (ASAS). Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. *Ann Rheum Dis* 2018;77:1539–40.
3 Anderson JJ, Baron G, van der Heijde D, *et al*. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. *Arthritis Rheum* 2001;44:1876–86.

4 Ramiro S, van der Heijde D, van Tubergen A, *et al*. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. *Ann Rheum Dis* 2014;73:1455–61.
5 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.
6 Molnar C, Scherer A, Baraliakos X, *et al*. TNF blockers inhibit spinal radiographic progression in ankylosing spondylitis by reducing disease activity: results from the Swiss Clinical Quality Management cohort. *Ann Rheum Dis* 2018;77:63–9.
7 Molto A, López-Medina C, Van den Bosch FE, *et al*. Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial. *Ann Rheum Dis* 2021;80:1436–44.
8 Song I-H, Hermann K, Haibel H, *et al*. Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. *Ann Rheum Dis* 2011;70:590–6.
9 Sieper J, Lenaerts J, Wollenhaupt J, *et al*. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, part 1. *Ann Rheum Dis* 2014;73:101–7.
10 Landewé R, Sieper J, Mease P, *et al*. Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study. *Lancet* 2018;392:134–44.
11 Landewé RB, van der Heijde D, Dougados M, *et al*. Maintenance of clinical remission in early axial spondyloarthritis following certolizumab pegol dose reduction. *Ann Rheum Dis* 2020;79:920–8.
12 van der Heijde D, Dijkmans B, Geusens P, *et al*. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 2005;52:582–91.
13 Coates LC, Moverley AR, McParland L, *et al*. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet* 2015;386:2489–98.
14 Song IH, Poddubnyy DA, Rudwaleit M, *et al*. Benefits and risks of ankylosing spondylitis treatment with nonsteroidal antiinflammatory drugs. *Arthritis Rheum* 2008;58:929–38.
15 Dougados M, Simon P, Braun J, *et al*. ASAS recommendations for collecting, analysing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis. *Ann Rheum Dis* 2011;70:249–51.
16 Proft F, Muche B, Listing J, *et al*. Study protocol: COmparison of the effect of treatment with Nonsteroidal anti-inflammatory drugs added to anti-tumour necrosis factor a therapy versus anti-tumour necrosis factor a therapy alone on progression of StrUctural damage in the spine over two years in patients with ankyLosing spondylitis (CONSUL) – an open-label randomized controlled multicenter trial. *BMJ Open* 2017;7:e014591.
17 van der Heijde D, Ramiro S, Landewé R, *et al*. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017;76:978–91.
18 van der Heijde D, Song I-H, Pangan AL, *et al*. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. *Lancet* 2019;394:2108–17.
19 Poddubnyy D, Sieper J. What is the best treatment target in axial spondyloarthritis: tumour necrosis factor α, interleukin 17, or both? *Rheumatology* 2018;57:1145–50.
20 Kiltz U, van der Heijde D, Boonen A, *et al*. Development of a health index in patients with ankylosing spondylitis (ASAS HI): final result of a global initiative based on the ICF guided by ASAS. *Ann Rheum Dis* 2015;74:830–5.
21 Ward MM, Deodhar A, Gensler LS, *et al*. 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Care Res* 2019;71:1285–99.

Clemens von Pirquet

Clemens Scheinecker [1], Dietrich Kraft[2]

Handling editor Gerd-Rüdiger R Burmester

[1]Rheumatology, Medizinische Universität Wien, Wien, Austria
[2]General and Experimental Pathology, Medizinische Universitat Wien, Wien, Austria

Correspondence to
Professor Clemens Scheinecker, Rheumatology, Medizinische Universität Wien, Wien 1090, Austria;
clemens.scheinecker@meduniwien.ac.at

Received 25 June 2021
Accepted 22 July 2021
Published Online First 6 August 2021

To cite: Scheinecker C, Kraft D. *Ann Rheum Dis* 2021;**80**:1370–1372.

Clemens Peter Freiherr von Pirquet, a great physician-scientist who described serum sickness and opened the field of allergy, was born in Hirschstetten near Vienna on 12 May 1874 into a distinguished family of the old Austrian-Hungarian empire (see figure 1). His father Peter Zeno von Pirquet held important positions in the Austrian parliament. His mother belonged to an assimilated Jewish banking family. After his school years in Vienna, Clemens, started theological studies on request of his mother, first at the University of Innsbruck and later at the Philosophical Faculty at the University of Leuven in Belgium. After having finished his theological studies with a master degree, he began to study medicine in Vienna and subsequently in Königsberg and Graz where he received his MD degree in 1900. After a military service, he started his training in paediatrics at the Charité in Berlin where he also met his future wife Maria Christina van Husen. In 1901, they returned to Vienna where he became junior doctor at the St. Anna Children's Hospital led by Theodor Escherich (1857–1911), who discovered the *Escherichia coli* bacteria. At the same time he worked with Rudolf Kraus, the first scientist to demonstrate precipitation of antibody and antigen at the Institute for Serotherapy at Vienna University.

Between 1903 and 1910, Pirquet made his most important, pioneering contributions investigating host reactions to foreign substances and thereby providing much of the foundation for today's modern immunology.

In 1905, he published the first fundamental analysis of the 'serum sickness'.[1] At that time, the established treatment of diphtheria infection was the application of an antiserum obtained from horses that had been immunised with diphtheria toxin. This therapy was protective against and was able to cure the disease but was also afflicted with side effects. Schick and von Pirquet recognised that non-human proteins contained in the antiserum can be mistaken by the immune system as harmful antigens. This leads to the production of antibodies that form immune complexes with these proteins and cause a disease of its own, later in 1963 classified as immune complex hypersensitivity (type III) reaction by Gell and Coombs.[2]

Pirquet and Schick described, in great detail, the course of symptoms that usually occurred around 14 days after exposure to the horse antitoxin and included fever, as high as 40°C, arthralgia/arthritis, urticaria-like skin manifestations, other rashes, lymphadenopathy, splenomegaly, leucopenia and hypotension. They suggested correctly that the symptoms are a consequence of the host response to a foreign substance rather than a direct consequence of the biologic agent or toxin itself.

By 1910, a more complete understanding of immunologic mechanisms was detailed by von Pirquet in his monograph "Allergie", a term that he coined, along with 'allergen', which he defined as an inciting agent or substance.[3] He proposed that the immune system can respond to an antigen (or allergen) in two different ways. One which induces immunity and protection and another one which causes an altered reactivity or sensitisation against the antigen. Pirquet showed how antigen and antibody, in the latter way, together form immune complexes which he postulated bind to a 'toxic physiologic product', today's complement. He even described the fell of serum complement titers during this reaction. Thus, with his studies he not only deciphered the pathophysiological mechanisms of serum sickness but at the same time his findings also explain diseases such as hay fever, anaphylaxis, asthma and immune complex-driven autoimmune diseases, most prominent among them are systemic lupus erythematodes and antineutrophil cytoplasmatic antibody (ANCA)-associated vasculitis. Even today's modern therapies sometimes are affected with side effects that relate to the immunological principles of serum sickness. This is the case for compounds that have been chemically modified with polyethylen glycol (PEG). For example, treatment with pegloticase, a recombinant PEGylated uricase approved for adults with refractory chronic gout, is associated with serious infusion reactions due to the development of high titers of antipegloticase antibodies.[4] Also, biological therapies, for example, with the anti-tumour necrosis factor (TNF) inhibitor infliximab, can cause serum sickness-like reactions.[5]

In 1907, Pirquet developed the simple and safe tuberculin skin test, also known as Pirquet reaction, for the (early) diagnosis of tuberculosis, at that time one of the most prevalent diseases, accounting for approximately 20% of deaths seen in the first and 40% of deaths in the second year of life among Viennese children. Moreover, by careful comparison of the results of the tuberculin test in children admitted to the paediatric department and groups of healthy children, he developed the concept of 'latent tuberculosis' which we still use today.[6]

For his achievements, he was nominated five times for the Nobel prize which he never received.

After his postdoctoral qualification in 1908 on the subject of vaccination,[7] (figure 2) he accepted an appointment as professor of paediatrics at the Johns-Hopkins University in Baltimore where he stayed for only 1 year because his income from his paediatric practice was too scarce. He then became head of the paediatrics department in Breslau in 1910. When Escherich died unexpectedly in 1911,

Figure 1 Photograph of Clemens von Pirquet.

Pirquet succeeded his mentor as Professor and Chair of Pediatrics at Vienna University.

After the years of world war I, Pirquet's scientific work, probably fueled by the precarious nutritional condition of children at that time, concentrated on studies of nutrition and anthropometrics. Pirquet also headed the League of Nations Child Welfare Committee and founded the Austrian Society for National Hygiene.[8]

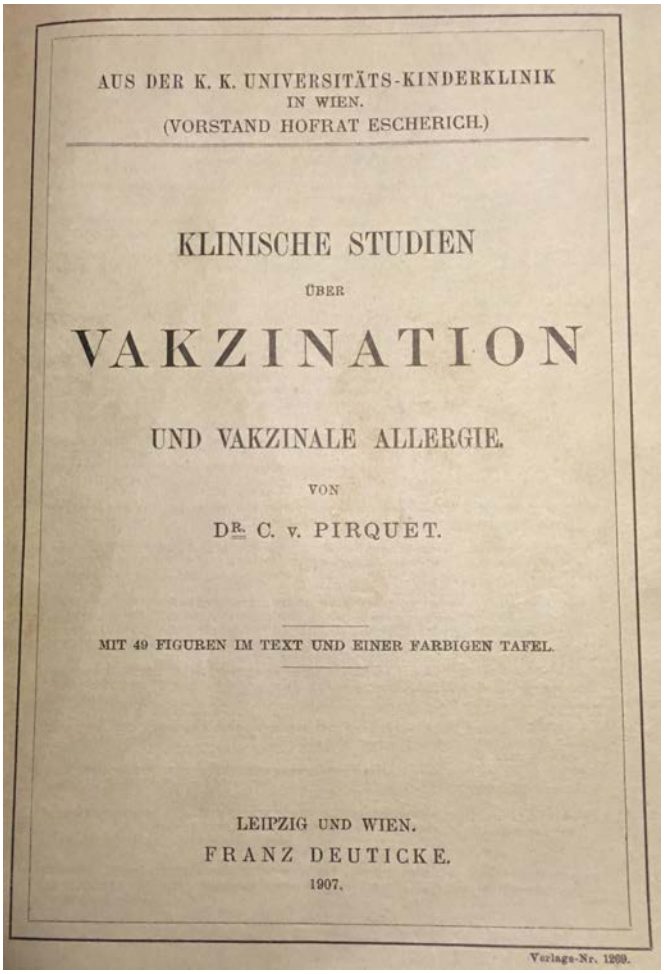
Besides, he was among the first scientists to found an educational department so study and treat children with organic brain damage and behavioural disorders.

In the 1920s Clemens von Pirquet was so famous to be nominated as presidential candidate of the young first republic of Austria, which he regarded as a dream rather than a serious possibility.

In 1927, at the peak of his career, he looked back on his former conclusions and stated:

'When after many years I look back on my earlier work, I am happy to state that none of the conclusions which I then labeled as positive and reliable were false. The term serum sickness and the concepts of allergy and antigen-antibody reaction have been generally accepted. The vast literature on those subjects which have since been published does not nullify the postulates and observations I made at that time. The finding of most practical importance, the cutaneous tuberculin test, is used by pediatricians all over the world with the same interpretations I devised years ago; and the diphtheria test discovered by my coworker, Bela Schick, has become a common tool of the medical profession. Both tests have rendered fundamental service in the understanding of tuberculosis and diphtheria'.[9]

In contrast to his professional success it seems that he was not blessed with a happy private life. His wife was never fully accepted by his family and suffered from a mental disorder and drug dependency. On 28 February 1929, Clemens von Pirquet, together with his wife, committed suicide for unknown reasons. His unstable financial situation, his relationship with his wife, family issues or his personal instability or desperation have been mentioned as potential motives.[8] His long-standing rival and


AUS DER K. K. UNIVERSITÄTS-KINDERKLINIK
IN WIEN.
(VORSTAND HOFRAT ESCHERICH.)

KLINISCHE STUDIEN
ÜBER
VAKZINATION
UND VAKZINALE ALLERGIE.
VON
DR. C. v. PIRQUET.

MIT 49 FIGUREN IM TEXT UND EINER FARBIGEN TAFEL.

LEIPZIG UND WIEN.
FRANZ DEUTICKE.
1907.

Verlags-Nr. 1269.

Figure 2 Pirquets postdoctoral thesis on the subject of vaccination which he strongly supported.

Figure 3 Statue of Clemens von Pirquet in front to the present Children's Department of the General Hospital of Vienna.

Figure 4 Former Children's Department of the General Hospital of Vienna.

successor Franz Hamburger, who was an ardent nationalist and later member of the Austrian Nationalsocialist Party, tragically abolished many of the concepts introduced by Pirquet, particularly everything to do with allergies and nutrition schemes.[10]

A statue of Clemens von Pirquet today stands in front of the present Children's Department of the General Hospital of Vienna (see figure 3).

The original Pirquet clinic with the famous lecture theatre survived until now in practically intact condition (see figure 4). Sadly, at present, there are plans to destroy the building because of expansion plans of the medical university. This would be a great misfortune since that building was the site of so many scientific discoveries. Its history argues for its preservation as a landmark in the advance of modern medicine.

In summary, Pirquet truly is one of the heroes and pillars of modern immunology and allergology due to his achievements as a highly innovative clinical and basic researcher, teacher and mentor for children's welfare.

Contributors Both authors have designed and written the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

ORCID iD
Clemens Scheinecker http://orcid.org/0000-0002-1828-2988

REFERENCES

1 Pirquet C, Schick B. *Die Serumkrankheit*. Leipzig u Wien, 1905.
2 Gell P, Coombs R. *Clinical aspects of immunology*. Oxford: Blackwell, 1963.
3 Pirquet C. Allergie. *Muenchner Med Wochenschrift* 1906;53:1457–8.
4 Lipsky PE, Calabrese LH, Kavanaugh A, *et al*. Pegloticase immunogenicity: the relationship between efficacy and antibody development in patients treated for refractory chronic gout. *Arthritis Res Ther* 2014;16:R60.
5 Vermeire S, Van Assche G, Rutgeerts P. Serum sickness, encephalitis and other complications of anti-cytokine therapy. *Best Pract Res Clin Gastroenterol* 2009;23:101–12.
6 Pirquet C. Frequency of tuberculosis in childhood. *JAMA* 1909;52:675–8.
7 Pirquet C. *Klinische Studien über Vakzination und vakzinale Allergie*. Franz Deuticke-Leipzig und Wien, 1907.
8 Shulman ST. Clemens von Pirquet: a remarkable life and career. *J Pediatric Infect Dis Soc* 2016;52:piw063.
9 Wagner R. *Clemens von Pirquet: his life and work*. Baltimore, MD: Johns Hopkins Press, 1968.
10 Breiteneder H, Hendler P-N, Kraft D. Legends of allergy and immunology: Clemens von Pirquet. *Allergy* 2020;75:1276–7.

Ultrasound definition of enthesitis in spondyloarthritis and psoriatic arthritis: arrival or starting point?

Emilio Filippucci , Gianluca Smerilli , Andrea Di Matteo , Walter Grassi

Handling editor Josef S Smolen

Rheumatology Unit, Department of Clinical and Molecular Sciences, "Carlo Urbani" Hospital, Polytechnic University of Marche, Jesi, Italy

Correspondence to
Dr Emilio Filippucci, Rheumatology Unit, Polytechnic University of Marche - Department of Clinical and Molecular Sciences, "Carlo Urbani" Hospital, 60035 Jesi, Ancona, Italy;
emilio_filippucci@yahoo.it

Received 31 March 2021
Accepted 11 June 2021
Published Online First 25 June 2021

To cite: Filippucci E, Smerilli G, Di Matteo A, *et al*. *Ann Rheum Dis* 2021;**80**:1373–1375.

ABSTRACT

Enthesitis has a key role in the diagnosis, classification and management of patients with spondyloarthritis and psoriatic arthritis. Clinical assessment of enthesitis is known to be inaccurate mainly due to its poor specificity. In this context, ultrasound has the potential to improve the evaluation of enthesitis and, therefore, the management of patients with spondyloarthritis and psoriatic arthritis. In this viewpoint, we review the Outcome Measures in Rheumatology (OMERACT) definitions for ultrasound enthesitis, highlighting their current limits and potential implications on rheumatology research and clinical practice.

INTRODUCTION

Ensuring standardisation in medical research is a challenging and virtually endless process, which requires the active contribution of the experts in the field who reach an agreement on how to assess a pathological condition and guarantee its updating.

Enthesitis has a key role in the diagnosis, classification and management of patients with spondyloarthritis (SpA) and psoriatic arthritis (PsA).[1 2]

Clinical assessment of enthesitis is known to be inaccurate mainly due to its poor specificity (eg, pain due to fibromyalgia). In this context, ultrasound (US) may improve the assessment of enthesitis, and, therefore, the diagnosis and management of patients with SpA and PsA.

In this viewpoint, we review the Outcome Measures in Rheumatology (OMERACT) definitions for US enthesitis, highlighting their current limitis and potential implications on rheumatology research and clinical practice.

TIMELINE OF US ENTHESITIS

In the last 15 years, the OMERACT US Task Force has taken considerable effort to improve the standardisation of US assessment of entheseal involvement in patients with SpA and PsA[3–6] and several goals were achieved.

The first milestone dates back to 2005 with the publication of the preliminary definition for US enthesopathy, which included all the main abnormalities detectable by US and laid the foundations for further international research.[3]

In 2011, a systematic literature review undertaken by the OMERACT group showed the lack of consensus on US examination (ie, scanning methods to use and number of entheses to assess), and the need to determine an US definition of enthesitis.[4]

In 2014, Terslev *et al* reached an agreement on the individual elementary lesions to include in the definition of US enthesitis.[5] Six elementary components of US enthesitis were identified, re-defined and divided in US findings indicative of 'active' entheseal inflammation (hypoechogenicity, thickening and power Doppler signal) or 'structural damage' (bone erosions, enthesophytes and calcifications).

A few years later, in 2018, the following final US definition of enthesitis in SpA and PsA was proposed by the OMERACT group: 'hypoechoic and/or thickened insertion of the tendon close to the bone (within 2 mm from the bony cortex), which exhibits Doppler signal if active and which may show erosions and enthesophytes/calcifications as a sign of structural damage'.[6]

OMERACT DEFINITIONS OF US ENTHESITIS: RECENT DATA ON CONTROLS

In the last 2 years, three studies obtained data at the large entheses of healthy subjects using the 2014 OMERACT US definitions developed by Terslev *et al*.[5] The results of these three studies converged in detecting a remarkably high prevalence of pathological findings at subject level, being entheseal thickening and enthesophytes the most frequent, and Doppler signal and bone erosions those with the lowest prevalence. Guldberg-Møller *et al* found an US elementary lesion in at least one enthesis in 47 (73.4%) out of the 64 studied subjects,[7] Bakirci *et al* detected entheseal thickening and enthesophytes, respectively, in 69 (86.3%) and 70 (87.5%) out of the 80 participants[8] and Di Matteo *et al* found the prevalence of entheseal thickening significantly higher than the one of hypoechogenicity both at subject and at entheseal level.[9] Finally, in a recent study by Falsetti *et al*, conducted in a cohort of 50 dysmetabolic patients, entheseal thickening and hypoechogenicity were found in at least one enthesis in more than two-thirds of the patients.[10] Conversely, the number of entheses with positive Doppler signal was low in all these studies, namely, 4 (1.25%) out of 320 entheses in Guldberg-Møller *et al*'s study, 11 (1.15%) out of 960 entheses in the Bakirci *et al*'s study, 11 (1.34%) out of 820 entheses in Di Matteo *et al*'s study, and 6 (1%) out of 600 entheses in the Falsetti *et al*'s study.

The high prevalence of US enthesitis in healthy subjects questions the diagnostic accuracy and discriminant power of the OMERACT US definitions of 'active' inflammation at the enthesis. Moreover, taking literally the 2018 OMERACT US Task Force definition of enthesitis may entail a number of potential misinterpretations.

First, either hypoechogenicity or thickening is necessary and sufficient to detect enthesitis. As such, this would lead to a dramatic overestimation of the prevalence US enthesitis (figure 1A).

Second, even though included among the 'inflammatory findings', Doppler signal is somehow

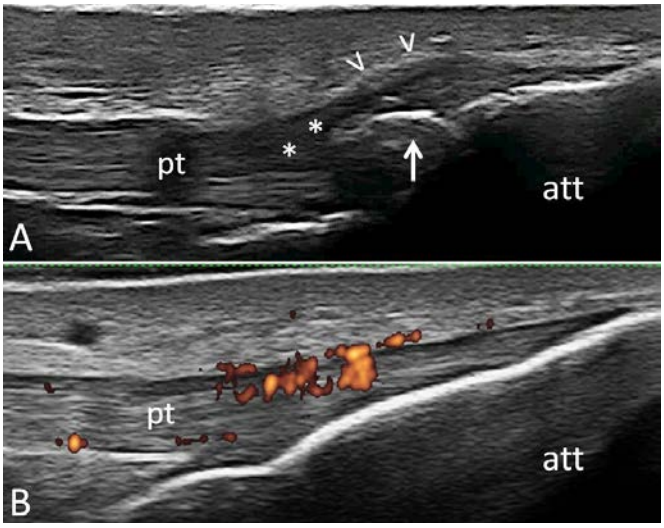


Figure 1 (A) Metabolic syndrome: longitudinal scan of patellar tendon at its distal insertion into the anterior tibial tuberosity. Note the presence of hypoechoic areas (asterisks), entheseal thickening (arrowheads) together with an enthesophyte (arrow). (B) Psoriatic arthritis: while no B-mode signs of enthesitis are detectable, the image shows evidence of intense power Doppler signal at the entheseal area. att, anterior tibial tuberosity; pt, patellar tendon.

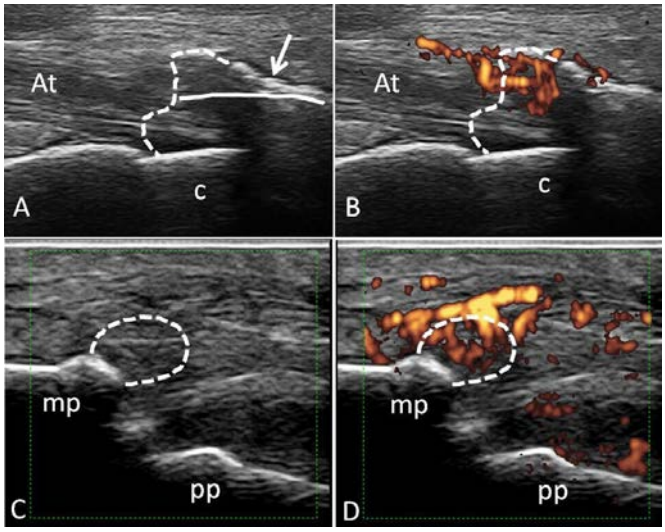


Figure 2 Psoriatic arthritis. Longitudinal scan of Achilles (A and B) and extensor finger (C and D) entheseal insertions, in B-mode and power Doppler ultrasound. (A and B) Achilles enthesitis. The dashed line represents 2-mm distance around the bony surface of the enthesis that considers the pathological presence of the enthesophyte (arrow). The solid line represents the border of the enthesis area without the enthesophyte. (C and D) Finger extensor enthesitis at the base of the middle phalanx (mp). The dashed line represents 2-mm distance around the bony surface of the enthesis. At, Achilles tendon; c, calcaneal bone; pp, proximal phalanx.

weighted differently. In fact, only Doppler mode can assess whether an enthesitis is active or not, but the presence of Doppler signal without B-mode findings is apparently not sufficient to define enthesitis.

The third and last unclear aspect regards the structural damage, which appears to be exclusively a bone-related matter; in fact, calcifications (the only finding accepted among the structural components related to the tendon side of the enthesis) were merged with the enthesophytes. Indeed, tendon damage within 2 mm from the cortical bone insertion does not have an US equivalent in this definition.

OPEN ISSUES AND POSSIBLE SOLUTIONS

Recent data on controls and a literal interpretation of the 2018 OMERACT US definition of enthesitis prompt out the following considerations.

First, the high prevalence of the B-mode findings defining enthesitis (ie, entheseal thickening and hypoechogenicity) in healthy subjects undermines their specificity and raises the need for refining the 2018 OMERACT definition. This could be obtained by adding quantitative measures (ie, cut-off values for entheseal thickening and Doppler score higher than 1). The Glasgow Ultrasound Enthesitis Scoring System (GUESS) and MAdrid Sonographic Enthesitis Index (MASEI), the most widely used scores for US enthesitis, have introduced cut-offs for measuring entheseal thickening.[11 12] However, the known variability of tendons and ligaments thickness among individuals is a potential limitation to the systematic application of these cut-offs. Therefore, further investigations are needed to identify potential 'confounders' of entheseal thickening (eg, age, sex, body mass index and physical activities) and adjust cut-off values accordingly. A possible alternative could be the combinations of qualitative findings forming patterns of entheseal involvement distinctive of SpA/PsA; whether a combination of hypoechogenicity or thickening and Doppler improves the accuracy of a correct diagnosis in comparison to Doppler alone will be a matter of further research.

Second, Doppler signal has shown the highest specificity among the entheseal US inflammatory findings as well as a high sensitivity in detecting even a small amount of abnormal blood flow. Thus, the presence of Doppler signal alone (ie, without hypoechoic areas or entheseal thickening) should also be regarded as sufficient to define enthesitis, and not only to state its 'activity' (figure 1B). Indeed, this would arguably improve the diagnostic potential of US in patients with suspected SpA/PsA, especially in the early phases of enthesitis or when the clinical examination of the entheses is not conclusive. Moreover, focusing the research of Doppler findings only at entheseal level may lead to discarding the precious information, because Doppler signal can also be detected outside the 2-mm area in patients with SpA.[13–15] Thus, in the presence of Doppler signal close to tendon-to-bone (or ligament-to-bone) insertion, also Doppler signal at tendon, ligament and/or bursal level should be considered an expression of active enthesitis. Moreover, enthesophytes disrupt the tendon-to-bone insertion line and focally move it proximally. This aspect may affect inter-observer reliability in the identification of the "entheseal area of interest", and requires a clear statement to avoid individual interpretations. We believe that together with the bony edge also the area where to detect specific abnormalities due to enthesitis should move proximally, and Doppler signal should be measured accordingly (figure 2A,B).

However, Doppler signal can be observed also after intense physical activity, or in patients with tendinous tears ('reparative Doppler').[16 17] Therefore, these possible predisposing conditions should always be investigated in the presence of Doppler signal at the enthesis; such finding should prompt a thorough US examination of the entire enthesis and tendon to rule out possible concomitant tears.

Third, hypoechoic areas and entheseal thickening have been frequently found in association with US findings of structural

damage, such as calcifications and enthesophytes.[9] This suggests that hypoechoic areas and entheseal thickening do not necessarily reflect only inflammation, but they may also be the expression of a reparative process at the tendon side of the enthesis. Indeed, it is known that these two mechanisms (ie, inflammation and degeneration) are not mutually exclusive, but might contribute together to the pathogenesis of tendinopathies/enthesopathies.[18 19]

NEW TECHNOLOGY AND SMALL ENTHESES

Finally, we must take note that the recent availability of very high frequency probes (ie, up to 24 MHz) allowed the assessment of small entheses of the hands (ie, insertions of finger extensor and flexor tendons, and pulleys), which have been demonstrated to be potential important targets of SpA (figure 2C,D).[20–22]

Such entheses might provide the opportunity to investigate sites expected to be less frequently exposed to the effect of concomitant metabolic syndrome and/or biomechanical forces in runners.

However, since the work of the OMERACT group referred on experience and data acquired in large entheses, whether the US findings and methods described and validated by that work can be applied sic et simpliciter to assess small entheses remains an open question.

CONCLUSIONS

In conclusion, we believe that the 2018 OMERACT definition of enthesitis represents the achievement of an important goal. In fact, it is the result of a standardised stepwise validation procedure, which led a large group of international experts to agree on how to define enthesitis by US. Research agenda should include an update and review process of this definition, also in light of recently published scientific evidence, mainly acquired in healthy subjects, that questioned its diagnostic accuracy and potential clinical impact. Such update should also clarify those aspects that may generate misinterpretation of US findings of enthesitis, thus affecting inter-observer reliability. This represents a prerequisite for conducting multicentre studies.

Finally, further research is required to test the potential value of the OMERACT definition at small entheses level.

Contributors All authors contributed to this viewpoint conception and design. Images preparation was performed by EF, GS and ADM. The first draft of the manuscript was written by EF and all the authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests EF has received speaking fees from AbbVie, Amgen, BMS, Janssen, Lilly, Novartis, Roche, Pfizer and UCB Pharma. WG has received speaking fees from Celltrion and Pfizer. All other authors declare no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Emilio Filippucci http://orcid.org/0000-0002-7251-7784
Gianluca Smerilli http://orcid.org/0000-0002-3972-4458
Andrea Di Matteo http://orcid.org/0000-0003-0867-7051

REFERENCES

1 Gossec L, Baraliakos X, Kerschbaumer A, *et al*. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* 2020;79:700.1–12.
2 Coates LC, Kavanaugh A, Mease PJ, *et al*. Group for research and assessment of psoriasis and psoriatic arthritis 2015 treatment recommendations for psoriatic arthritis. *Arthritis Rheumatol* 2016;54:n/a–71.
3 Wakefield RJ, Balint PV, Szkudlarek M, *et al*. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005;32:2485–7.
4 Gandjbakhch F, Terslev L, Joshua F, *et al*. Ultrasound in the evaluation of enthesitis: status and perspectives. *Arthritis Res Ther* 2011;13:R188.
5 Terslev L, Naredo E, Iagnocco A. Outcome measures in rheumatology ultrasound Task force. defining enthesitis in spondyloarthritis by ultrasound: results of a Delphi process and of a reliability reading exercise. *Arthritis Care Res* 2014;66:741–8 https://pubmed.ncbi.nlm.nih.gov/24151222/
6 Balint PV, Terslev L, Aegerter P, *et al*. Reliability of a consensus-based ultrasound definition and scoring for enthesitis in spondyloarthritis and psoriatic arthritis: an OMERACT us initiative. *Ann Rheum Dis* 2018;77:1730–5.
7 Guldberg-Møller J, Terslev L, Nielsen SM, *et al*. Ultrasound pathology of the entheses in an age and gender stratified sample of healthy adult subjects: a prospective cross-sectional frequency study. *Clin Exp Rheumatol* 2019;37:408–13.
8 Bakirci S, Solmaz D, Stephenson W, *et al*. Entheseal changes in response to age, body mass index, and physical activity: an ultrasound study in healthy people. *J Rheumatol* 2020;47:968–72.
9 Di Matteo A, Filippucci E, Cipolletta E, *et al*. How normal is the enthesis by ultrasound in healthy subjects? *Clin Exp Rheumatol* 2020;38:472–8.
10 Falsetti P, Conticini E, Baldi C, *et al*. High prevalence of ultrasound-defined enthesitis in patients with metabolic syndrome. Comment on: how normal is the enthesis by ultrasound in healthy subjects? di Matteo et al. *Clin Exp Rheumatol* 2021;39:435–6.
11 Balint PV, Kane D, Wilson H, *et al*. Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. *Ann Rheum Dis* 2002;61:905–10.
12 de Miguel E, Cobo T, Muñoz-Fernández S, *et al*. Validity of enthesis ultrasound assessment in spondyloarthropathy. *Ann Rheum Dis* 2009;68:169–74.
13 Macía-Villa C, Falcao S, Medina J, *et al*. Ultrasonography of enthesis in psoriatic arthritis: a descriptive and reliability analysis of elemental lesions and power Doppler subtypes. *Scand J Rheumatol* 2019;48:454–9.
14 Naredo E, Batlle-Gualda E, García-Vivar ML, *et al*. Power Doppler ultrasonography assessment of enteses in spondyloarthropathies: response to therapy of entheseal abnormalities. *J Rheumatol* 2010;37:2110–7.
15 Filippucci E, Aydin SZ, Karadag O, *et al*. Reliability of high-resolution ultrasonography in the assessment of Achilles tendon enthesopathy in seronegative spondyloarthropathies. *Ann Rheum Dis* 2009;68:1850–5.
16 Proft F, Grunke M, Reindl C, *et al*. The influence of long distance running on sonographic joint and tendon pathology: results from a prospective study with marathon runners. *BMC Musculoskelet Disord* 2016;17:272.
17 Alfredson H, Masci L, Ohberg L. Partial mid-portion Achilles tendon ruptures: new sonographic findings helpful for diagnosis. *Br J Sports Med* 2011;45:429–32.
18 Abate M, Di Carlo L, Salini V, *et al*. Metabolic syndrome associated to non-inflammatory Achilles enthesopathy. *Clin Rheumatol* 2014;33:1517–22.
19 Abate M, Silbernagel KG, Siljeholm C, *et al*. Pathogenesis of tendinopathies: inflammation or degeneration? *Arthritis Res Ther* 2009;11:235.
20 Zabotti A, Idolazzi L, Batticciotto A, *et al*. Enthesitis of the hands in psoriatic arthritis: an ultrasonographic perspective. *Med Ultrason* 2017;19:438–43.
21 Tinazzi I, McGonagle D, Zabotti A, *et al*. Comprehensive evaluation of finger flexor tendon entheseal soft tissue and bone changes by ultrasound can differentiate psoriatic arthritis and rheumatoid arthritis. *Clin Exp Rheumatol* 2018;36:785–90.
22 Smerilli G, Cipolletta E, Di Carlo M, *et al*. Power Doppler ultrasound assessment of A1 Pulley. A new target of inflammation in psoriatic arthritis? *Front Med* 2020;7:204.

TRANSLATIONAL SCIENCE

Comparison of two dose escalation strategies of methotrexate in active rheumatoid arthritis: a multicentre, parallel group, randomised controlled trial

Siddharth Jain,[1] Varun Dhir ,[1] Amita Aggarwal,[2] Ranjan Gupta,[3] Bidyalaxmi Leishangthem,[1] Shankar Naidu ,[1] Aastha Khullar,[1] Supriya Maurya,[2] Veena Dhawan,[4] Shefali Khanna Sharma,[1] Aman Sharma,[1] Sanjay Jain[1]

Handling editor Josef S Smolen

► Additional online supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220512).

[1]Division of Clinical Immunology and Rheumatology, Department of Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India
[2]Department of Clinical Immunology and Rheumatology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India
[3]Department of Rheumatology, All India Institute of Medical Sciences, New Delhi, India
[4]Department of Experimental Medicine and Biotechnology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Correspondence to
Dr Varun Dhir, Department of Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India; varundhir@gmail.com

SJ and VD are joint first authors.

Received 6 April 2021
Accepted 25 May 2021
Published Online First 10 June 2021

To cite: Jain S, Dhir V, Aggarwal A, *et al*. *Ann Rheum Dis* 2021;**80**:1376–1384.

ABSTRACT

Objectives There are no head-to-head trials of different dose escalation strategies of methotrexate (MTX) in RA. We compared the efficacy, safety and tolerability of 'usual' (5 mg every 4 weeks) versus 'fast' (5 mg every 2 weeks) escalation of oral MTX.

Methods This multicentre, open-label (assessor blinded) RCT included patients 18-55 years of age having active RA with disease duration <5 years, and not on DMARDs. Patients were randomized 1:1 into usual or fast escalation groups, both groups starting MTX at 15 mg/week till a maximum of 25 mg/week. Primary outcome was EULAR good response at 16 weeks, secondary outcomes were ΔDAS28 and adverse effects (AE). Analyses were intention-to-treat.

Results 178 patients with mean DAS28-CRP of 5.4(1.1) were randomized to usual (n=89) or fast escalation groups (n=89). At 16 weeks, there was no difference in good EULAR response in the usual (28.1%) or fast escalation (22.5%) groups (p=0.8). There was no difference in mean ΔDAS28-CRP at 8 weeks (-0.9, -0.8, p=0.72) or 16 weeks (-1.3, -1.3, p=0.98). Even at 24 weeks (extended follow-up), responses were similar. There were no inter-group differences in ΔHAQ, or MTX-polyglutamates 1-3 levels at 8 or 16 weeks. Gastrointestinal AE were higher in the fast escalation group over initial 8 weeks (27%, 40%, p=0.048), but not over 16 weeks. There was no difference in cytopenias, transaminitis, or drug discontinuation/dose reduction between the groups. No serious AE were seen.

Conclusion A faster MTX escalation strategy in RA was not more efficacious over 16-24 weeks, and did not significantly increase AE, except higher gastrointestinal AE initially.

Trial registration number CTRI/2018/12/016549

Key messages

What is already known about this subject?

- Although guidelines suggest a 'fast' escalation of methotrexate (MTX) in rheumatoid arthritis (RA) (the 3E initiative recommends escalating by 5 mg every 2 or 4 weeks; European League against Rheumatism 2019 recommends reaching maximal MTX dose by 4–6 weeks), there have been no head-to-head trials.

What does this study add?

- First randomised controlled trial on two different escalation strategies of oral MTX in RA, comparing usual (5 mg every 4 weeks) to fast (5 mg every 2 weeks) escalation after starting at 15 mg per week.
- No difference in efficacy at 16 weeks (or at the 24 weeks extended efficacy end point) nor any difference in MTX-mono/di/triglutamate levels at 8 or 16 weeks.
- No difference in cytopaenias, transaminitis, serious adverse effects (AEs), drug discontinuation or dose reduction, but higher gastrointestinal AE in the initial 8 weeks with fast escalation.

How might this impact on clinical practice or future developments?

- There seems to be no additional benefit gained in terms of efficacy by escalating MTX faster than 5 mg every 4 weeks, when started at 15 mg. Although faster escalation does lead to higher gastrointestinal AE initially, it does not translate into increased drug discontinuation or dose reduction.

INTRODUCTION

The current therapeutic paradigm for rheumatoid arthritis (RA) involves starting with methotrexate (MTX) monotherapy for 4–6 months, followed by addition of other disease modifying antirheumatic drugs (DMARDs) in case low disease activity (LDA) or remission is not achieved.[1 2] When optimally used, 30%–40% of patients are able to achieve this target with MTX alone.[3 4] However, in the real world, response rates are much worse because of suboptimal MTX use, which leads to premature addition of other DMARDs including biologics.[5] To avoid the associated incremental costs and adverse effects (AEs), it is crucial to optimise initial MTX monotherapy.

One strategy to optimise MTX is by quickly reaching its maximum dose and allowing patients to receive this dose for at least 8–12 weeks. This can be accomplished either by starting at higher doses,

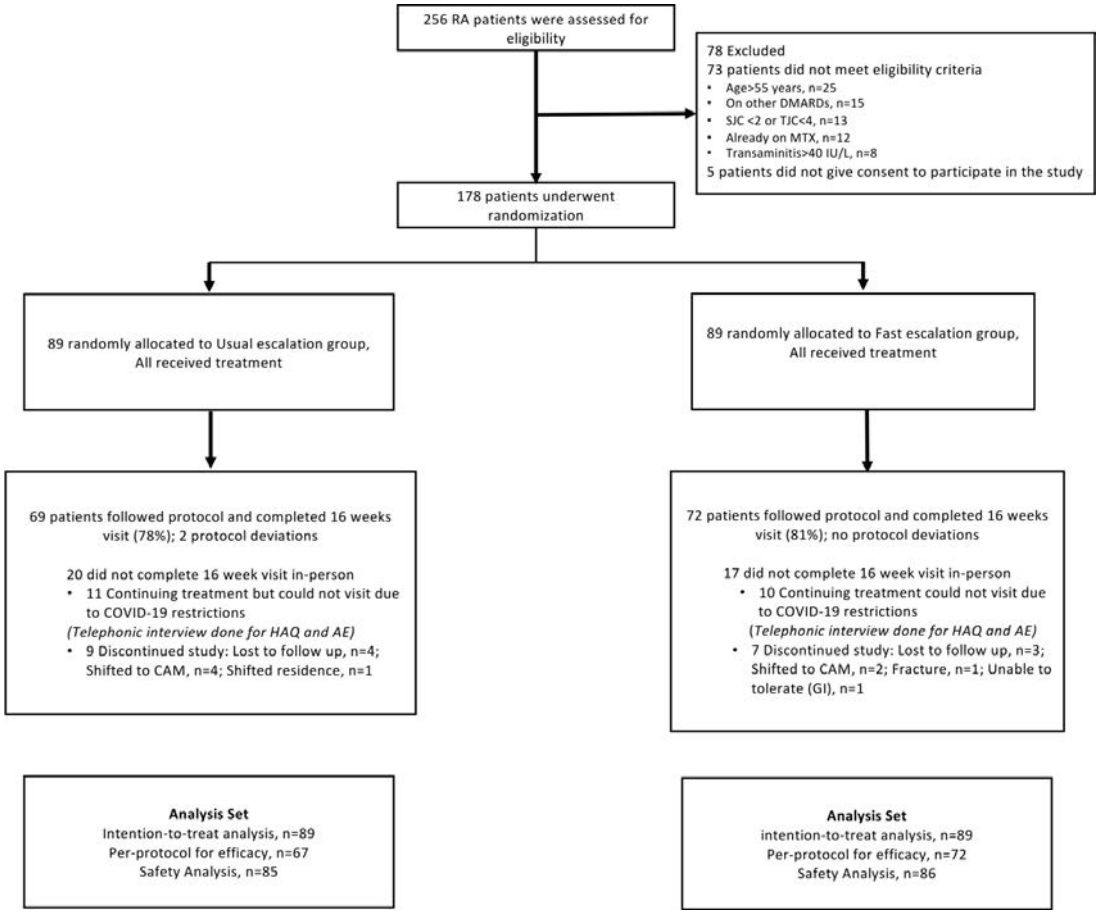


Figure 1 Flow chart showing disposition of participants in the study. AE, adverse effects; CAM, complementary and alternative medications; HAQ, Health Assessment Questionnaire; GI, gastrointestinal; MTX, methotrexate; SJC, swollen joint count (28 joints); TJC, tender joint count.(28 joints)

or by faster escalation, or a combination of both. The first of these, that is, starting at a higher dose of 15 mg, rather than the traditional 7.5 mg, has been endorsed by guidelines and is increasingly used in those without safety concerns.[6]

However, a large degree of variability exists in the escalation of MTX, with dose increase by 5–15 mg every 2–8 weeks in contemporary randomised controlled trials (RCTs).[3 7 8] There is a lack of a clear escalation protocol, with the 3E initiative recommending escalation by 5 mg every two or 4 weeks, and European League against Rheumatism (EULAR) recommending achieving full MTX dose by 4–6 weeks.[1 6] Although a rapid escalation may lead to a faster and better response, it also carries a higher risk of intolerance (thus dropouts) and AEs like cytopaenia, pneumonitis or transaminitis. Thus, there remains apprehension and poor utilisation of fast escalation among clinicians, which is driven by a lack of head-to-head trials in this area.

Thus, we planned the Methotrexate Escalation In Rheumatoid Arthritis (MEIRA), an RCT to compare the effect of two different escalation strategies, 'usual' (5 mg every 4 weeks) or 'fast' (5 mg every 2 weeks) of oral MTX started at a dose of 15 mg in both groups, on efficacy, tolerability and AE over 16 weeks in patients with active RA.

METHODOLOGY

Study design and trial overview

MEIRA was a pragmatic, investigator initiated, open-label (assessor blinded), parallel-group RCT that compared two escalation schedules of oral MTX over 16 weeks. All patients gave written informed consent prior to their inclusion in the study. The recruitment period extended from 15 January 2019 to 18 March 2020, and final data collection occurred on 30 October 2020. The upper limit of age for recruitment was increased from 50 to 55 years and an extended post-trial efficacy visit at 24 weeks was added after commencement of the trial (20 November 2019).

Participants

Eligible patients were 18–55 years old, having active RA with four or more tender joints, and two or more swollen joints, being MTX-naïve or off MTX for at least 6 months and having a disease duration of less than 5 years. They could be on low-dose prednisolone (<10 mg/day) and/or hydroxychloroquine but not other DMARDs. All patients fulfilled the 2010 American College of Rheumatology (ACR)/EULAR classification criteria for RA.[9] (Detailed inclusion and exclusion criteria are given in online supplemental file 1.

Randomisation, allocation concealment and blinding

The trial participants were randomised 1:1 through variable block (block size of 4, 6 and 8) randomisation stratified by centre, using an online random number generator (http://www.randomization.com). Allocation concealment was done using serially numbered opaque sealed envelopes. The trial participants and the healthcare providers (SJ/SM) recruiting them and dispensing the study drug were not blinded to the intervention; however, joint counts were assessed by a blinded assessor (VD/SN/AA/RG).

Intervention

Oral MTX was started at a dose of 15 mg once a week in both groups and escalated by either 5 mg every 4 weeks

Table 1 Baseline demographic and clinical characteristics of the included patients (n=178)

Characteristic, mean±SD except where specified	Total (n=178)	Usual escalation (n=89)	Fast escalation (n=89)
Age, years	39.8±8.6	39.3±8.7	40.2±8.5
Gender, female, n (%)	149 (84)	74 (83)	75 (84)
Disease duration, years	1.9±1.4	1.7±1.3	2.0±1.5
<1 year, n (%)	86 (48)	42 (48)	44 (49)
1–2 years, n (%)	34 (19)	20 (23)	14 (19)
2–5 years, n (%)	57 (32)	26 (30)	31 (32)
Tender joint count 28 joints	17±7	17±7	17±7
Swollen joint count 28 joints	7±5	7±5	6±4
ESR, mm first hour	64±33	67±35	65±31
CRP, mg/L	24.0±28.2	26.5±27.7	21.5±28.6
HAQ	1.2±0.7	1.2±0.7	1.3±0.7
BMI, kg/m^2	24.8±4.7	24.3±4.8	25.4±4.6
DAS28-CRP	5.4±1.1	5.4±1.1	5.4±1.0
>5.1, n (%)	71 (40)	36 (41)	35 (39)
>3.2 to ≤5.1, n (%)	107 (60)	53 (60)	54 (61)
≤3.2	0	0	0
DAS28-ESR	6.3±0.9	6.4±1.0	6.3±0.9
RF positive, n (%)	149 (84)	75 (84)	74 (83)
CCP positive*, n (%)	137 (87)	69 (91)	68 (84)
Prednisolone, n (%)	17 (10)	9 (10)	8 (9)
Hydroxychloroquine, n (%)	15 (8)	9 (10)	6 (7)
Deformity, n (%)	17 (10)	13 (15)	4 (5)**

*Data of CCP were available in 157 patients (76+81).
†**p<0.05
.BMI, body mass index; CCP, antibody to cyclic citrullinated peptide; CRP, C reactive protein ; DAS28, Disease Activity Score 28 joint; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; RF, rheumatoid factor.

Table 2 Key efficacy outcomes (dichotomous) as percentages at 8 and 16 weeks in the usual and fast MTX escalation groups (intention to treat)

	Fast escalation (n=89)	Usual escalation (n=89)	OR* fast versus usual (95% CI)	P value
EULAR response†				
W8 good response	11.2	10.1	1.1 (0.4 to 2.9)	0.8
W16 good response (primary outcome)	22.5	28.1	0.7 (0.4 to 1.5)	0.39
W8 good or moderate response	47.2	52.8	0.8 (0.4 to 1.4)	0.45
W16 good or moderate response	65.2	61.8	1.2 (0.6 to 2.1)	0.64
DAS28-CRP-based responses				
W8 remission	7.9	4.5	1.8 (0.5 to 6.2)	0.54
W16 remission	14.6	13.5	1.1 (0.5 to 2.4)	0.80
W8 LDA or remission	12.4	14.6	0.8 (0.4 to 2.0)	0.82
W16 LDA or remission	27.0	29.2	0.9 (0.5 to 1.7)	0.74
W8-0 ΔDAS28 >1.2	33.7	33.7	1.0 (0.5 to 1.9)	1.0
W16-0 ΔDAS28 >1.2	53.9	55.1	1.0 (0.5 to 1.7)	0.82
Boolean 3-variable remission				
W16 remission	11.2	6.7	0.6 (0.2 to 1.6)	0.29
Based on HAQ‡				
W16-0 ΔHAQ >0.22	76.4	68.5	1.5 (0.8 to 2.9)	0.24
W16 HAQ <0.5	69.7	70.8	1.0 (0.5 to 1.8)	0.87

All values are given in percentages.
*OR of fast escalation to usual escalation.
†EULAR response based on DAS28-CRP (3variable).
‡By the Indian validated version of HAQ.
CRP, C reactive protein; DAS28, Disease Activity Score 28 joint; EULAR, European League against Rheumatism; HAQ, Health Assessment Questionnaire; LDA, low disease activity; MTX, methotrexate; W8, week 8; W16, week 16.

(usual escalation group) or every 2 weeks (fast escalation group), till a maximum dose of 25 mg once a week was reached, which was then continued till 16 weeks (detailed in online supplemental file 1). Folic acid was supplemented at a dose of 5 mg two times per week in all patients. If patients were on hydroxychloroquine or low-dose prednisolone at inclusion, this was continued. The use of non-steroidal anti-inflammatory drugs was permitted as per patients' requirements. Additionally, patients could receive one dose of intramuscular (80 mg) or intraarticular methylprednisolone acetate in the initial 4 weeks, based on the treating physician's discretion. After the completion of the study at 16 weeks, patients were continued to be followed up till 24 weeks, during which period addition of other DMARDs like hydroxychloroquine, leflunomide or sulfasalazine was permitted.

Study outcomes

The primary outcome was proportion of patients with good response (final Disease Activity Score 28 joint (DAS28) C reactive protein (CRP) ≤3.2 and fall >1.2, as per EULAR response criteria) at 16 weeks.[10]

Secondary outcomes (planned) included change in DAS28-CRP at 16 weeks and occurrence of symptomatic AEs and laboratory abnormalities (cytopaenias or transaminitis). Unplanned secondary outcomes included proportion of patients with good or moderate EULAR response (by DAS28-CRP), DAS28-CRP-based remission at 16 weeks, DAS28-CRP-based remission or LDA at 16 weeks, Boolean remission (three variable) at 16 weeks, change in Health Assessment Questionnaire (HAQ) over 16 weeks, achieving HAQ <0.5 at 16 weeks, change in HAQ >0.22, proportion of patients with dose reduction or drug discontinuation.

In addition, we also compared RBC MTX polyglutamate (1-3) levels between the groups at 8 and 16 weeks. These were measured using high-performance liquid chromatography (method detailed in online supplemental file 1).[11]

Study procedures

For assessing efficacy, the modified DAS using 28 joints (three variables), which is equivalent to the four-variable DAS28, was used.[10 12] This was preferred as visual analogue scale for global assessment is not easily understood by Indian patients.[13] Study visits for efficacy took place at 8 and 16 weeks (and 24 weeks). Physical function was assessed using the validated Indian version of HAQ (self or physician administered) at baseline and 16 weeks.[14] Symptomatic AEs were assessed using a questionnaire that included questions on occurrence of common AE (Questionnaire provided in the online supplemental file 1). Individual symptomatic AE were analysed separately as well as categorised by organ system (gastrointestinal (GI) or central nervous system (CNS)). Thus, symptomatic GI AE included occurrence of either nausea, vomiting, stomach discomfort, bad taste or loss of appetite, whereas, symptomatic CNS AE included occurrence of either lethargy, dizziness, irritability or anxiety. These were assessed at 4, 8 and 16 weeks visits. 'Any' symptomatic AE was defined as occurrence of any of these symptoms at least once (on any of the visits).

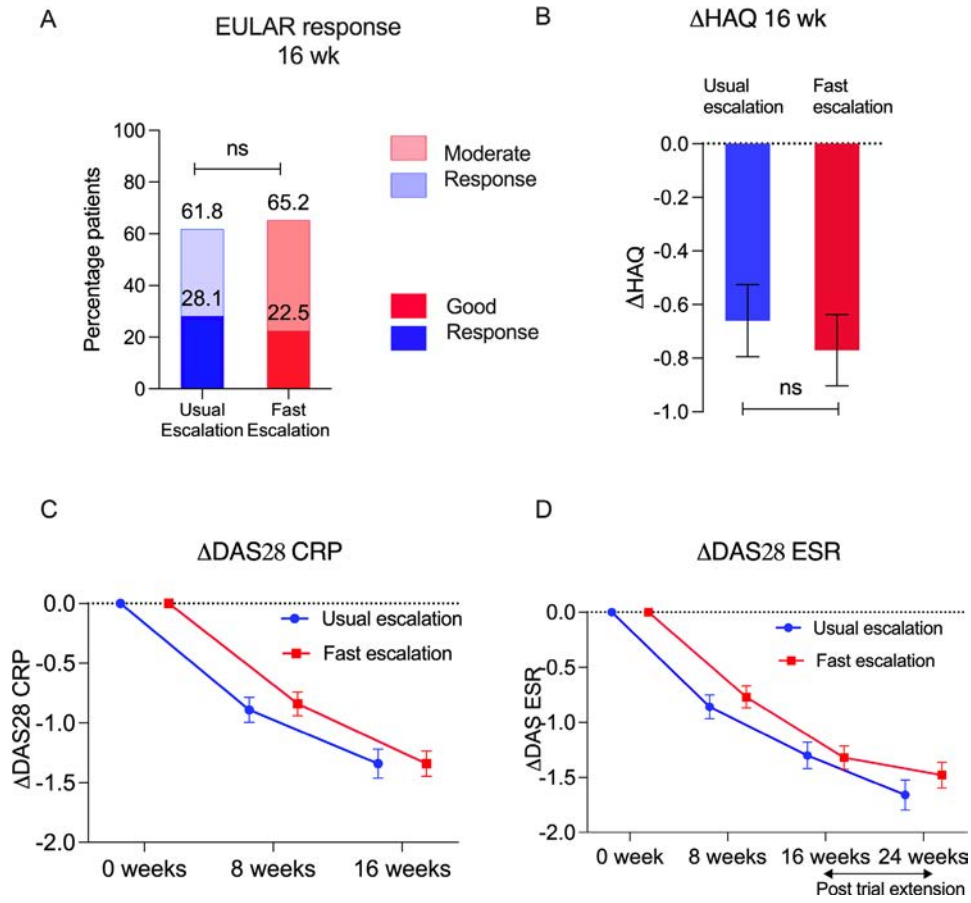


Figure 2 Major efficacy outcomes including EULAR response (good and/or moderate) at 16 weeks as per DAS28-CRP (A), change in Indian HAQ at 16 weeks (B) and change in DAS28-CRP (C) and DAS28-ESR (D) over time in the usual and fast methotrexate escalation groups (intention to treat). CRP, C reactive protein; DAS28, Disease Activity Score 28 joint; ESR, erythrocyte sedimentation rate; EULAR, European League against Rheumatism; HAQ, Health Assessment Questionnaire; ns, notsignificant.

Patients were monitored for pneumonitis, infections and serious AE including death and hospitalisation from any cause. Laboratory tests for safety including complete blood count and liver function tests were done every 2 weeks during MTX escalation and then 4–8 weekly. Leucopaenia was defined by a white blood cell count (WBC) <4 x 10^9/L and thrombocytopaenia as platelet count <100 x 10^9/L. Occurrence of any transaminitis referred to values of either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) above the upper limit of normal (40 IU/L), and transaminitis more than 2 x upper limit of normal (ULN) was defined as elevation more than twice that value, that is, values of either AST or ALT above 80 IU/L. Persistent transaminitis was defined as elevation on at least two occasions. The standard operating protocols followed in case of cytopaenia or transaminitis are provided in online supplemental file 1.

Effect of the SARS-CoV-2 pandemic

During the initial phase of the SARS-COV-2 pandemic, the government of India imposed a strict nationwide lockdown that lasted for 6 weeks, followed by gradual reopening.[15] In view of travel difficulties, some patients could not reach for joint count assessment at the 8 week (~20%) and 16 week visits (~12%). They were contacted telephonically, MTX was made available, and were continued in the study in the absence of any laboratory abnormalities. Recruitment to the study was stopped early due to COVID-19-related disruptions.

Statistical analysis

We calculated the sample size by using an expected primary outcome of EULAR good response in 20% and 40% (difference 20%) in the usual and fast escalation groups respectively at 16 weeks, with power of 90% and p value of 0.05 (G power V.3.1),[16] which gave a sample size of 234 (planned 300). With the actual sample size of 178, the power of the study reduced to 80%.

Primary analysis was intention to treat (ITT), with missing values imputed as worst outcomes for categorical variables and last observation carried forward for continuous variables. Multiple sensitivity analyses using different imputation methods (best outcome, last observation carried forward, completers, per-protocol, etc) were performed for the primary and secondary outcomes. We also performed a subgroup analysis (unplanned) of key outcomes in early RA (<2 years).

Categorical variables were summarised as percentages or proportions and analysed using the χ^2, or Fisher's exact test. Continuous variables were summarised as mean (SD) or median (range) and analysed using the Student's t-test (normally distributed data) or the Mann-Whitney U/Wilcoxon rank sum test (non-normally distributed data). Shapiro-Wilk test was used for testing of normality. Data were analysed using the SPSS (SPSS, V.26). Graphs were made using GraphPad Prism V.8 (GraphPad Software, California, USA). A two-tailed $p<0.05$ was considered statistically significant.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Participant flow and recruitment

Of the 256 patients with RA screened for this study, 178 were recruited and randomly assigned to receive usual (n=89) or fast escalation (n=89) of MTX. Among the screen failures, none were excluded due to prior intolerance to MTX. All randomised patients received at least one dose of the allocated treatment and were included in the ITT analysis. 141 patients completed the 16-week visit; 139 patients (78%) were included in per-protocol analysis. In addition, 21 (12%) patients who were following protocol but could not come for the 16-week visit due to COVID-19 restrictions, were interviewed telephonically for HAQ and AEs. A total of 171 (96%) patients completed at least one study visit and were evaluable for safety (figure 1).

Baseline demographics and characteristics

The majority of patients were females (149 (84%)). The mean age was 39.8 (8.6) years, and the mean disease duration was 1.9 (1.4) years. At the time of inclusion into the study, only 10% were receiving low-dose glucocorticoids or hydroxychloroquine, all had moderate-to-high disease activity and most (67%) had a disease duration of less than 2 years. Only 13 (7%) had previously been treated with MTX—all of them had received suboptimal doses of MTX (7.5–15 mg) for a short duration (3–6 months). The reason for non-continuation was mainly the lack of perceived efficacy leading to a switch to complementary and alternative medications; in no case was it due to MTX intolerance. The baseline disease characteristics are given in table 1. There was no significant difference between the two groups in any parameter, except slightly more deformities in the usual escalation group. Details about comorbidities are provided in online supplemental table S1. Forty (45%) patients each in the two groups received a single dose of intramuscular or intra-articular methylprednisolone acetate.

Primary outcome

The primary outcome of good response by EULAR criteria was not significantly different in the fast (22.5%) and usual escalation (28.1%, p=0.39) groups at 16 weeks (OR 0.7, 95% CI 0.4 to 1.4). (table 2, figure 2). Multiple sensitivity analysis, DAS28-erythrocyte sedimentation rate (ESR)-based EULAR response and subgroup analyses of early RA were consistent with the main analysis (online supplemental tables S2–S4).

Secondary outcomes

EULAR good or moderate response

Any response (good or moderate) by EULAR criteria was also not significantly different between the fast (65.2%) and usual (61.8%, p=0.64) escalation groups at 16 weeks (OR 1.2, 95% CI 0.6 to 2.1). (table 2, figure 2) Multiple sensitivity analysis, DAS28-ESR-based EULAR responses and subgroup analyses for early RA were consistent with the main analysis (online supplemental tables S2–S4).

Change in DAS28

DAS28-CRP declined by 1.3 in both groups (p=0.98) at 16 weeks (difference 0, 95% CI −0.3 to 0.3). (figure 2, online supplemental table S5) In the per-protocol population, the decline was −1.6 and −1.7 in the fast and usual escalation groups (difference 0.1, 95% CI −0.3 to 0.4). The decline in DAS28-ESR at 16 weeks was also the same in both groups of 1.3 (difference of 0, 95% CI −0.2 to 0.3). There was no significant inter-group difference in the individual components of DAS28 (online supplemental table S5).

Change in HAQ

There was a significant decline in HAQ in both the fast (−0.8) and usual (−0.7) escalation groups, however, there was no significant intergroup difference (difference −0.1, 95% CI −0.3 to 0.1, p=0.26) (online supplemental figure S1, online supplemental table S5). There was no significant difference in the proportion of patients with a clinically significant change of HAQ or normalisation of HAQ in the two groups (table 2).

DAS28-CRP-based remission or LDA and Boolean remission (unplanned)

There was no significant difference in the proportion of patients who achieved remission or LDA at 16 weeks between the two groups (table 2).

Extended efficacy analysis at 24 weeks

Similar proportion of patients required addition of another DMARD at 16 weeks in both groups (online supplemental table S6). At the post-trial extended follow-up at 24 weeks (118 patients, 66%), the mean DAS28-ESR (ITT) had declined by −1.5 and −1.7 (p=0.31) in the fast and usual escalation groups (difference 0.2, 95% CI −0.2 to 0.5), whereas the decline in the per-protocol population was −1.8 and −2.0 (p=0.22). There was no significant difference in the EULAR responses at 24 weeks (online supplemental table S3).

Safety

No serious AE including pneumonitis, serious infections or death occurred in this study. Leucopaenia (<4 x 10^9/L) and thrombocytopaenia (<100 x 10^9/L) were uncommon, occurring in 3 and 2 patients, and two patients in each group, respectively, in the fast and usual escalation groups. Transaminitis 2xULN (ALT or AST >80 IU/L) occurred in 7 and 6 patients in the fast and usual escalation groups. (table 3, figure 3). There was also no difference in the occurrence of any transaminitis (ALT or AST >40 IU/L) (table 3), or in the persistence of transaminitis (at least on two different visits) which occurred in 13 and 11 patients in the fast and usual escalation groups, respectively (p=0.84) Details of laboratory AE at individual time-points are given in online supplemental table S7.

There were significantly higher GI AEs in the fast escalation group (47%) compared with usual group (32%) in the first 8 weeks (difference 15 percentage, 95% CI 0.3 to 29, p=0.048) (figure 3A), however, this was non-significant over 16 weeks (figure 3B, table 3). There were no significant differences in individual GI or CNS AE at 16 weeks (table 3, figure 3) or at any specific time point (online supplemental table S8). Oral ulcers were numerically higher in the fast escalation group (table 3). Rates of MTX discontinuation, dose reduction and use of medicines to counteract AEs were similar in both groups (table 3). The number of patients reporting more than one symptomatic GI AE were also not significantly different between the groups (online supplemental table S9).

MTX polyglutamates

There was no significant difference in the MTX mono, di or triglutamate levels between the usual and fast escalation groups

Table 3 Adverse effects (AEs) during the study period (over 16 weeks) in the two methotrexate escalation groups

	Fast escalation N=86	Usual escalation N=85	OR (95% CI)	P value
Total AE	58 (68)	54 (64)	1.2 (0.6 to 2.3)	0.59
Serious AE	0	0	–	–
Drug discontinuation (AE related)	1 (1)	2 (2)	0.5 (0.1 to 5.5)	0.62
Dose reduction (AE related)	2 (2)	2 (2)	1.0 (0.1 to 7.2)	1.0
Difficulty in MTX dose escalation (AE related)	4 (5)	3 (4)	1.3 (0.3 to 6.1)	1.0
Symptomatic AE				
Any symptomatic AE*	56 (65)	50 (59)	1.3 (0.7 to 2.4)	0.40
Nausea	26 (30)	22 (26)	1.2 (0.6 to 2.4)	0.53
Vomiting	7 (8)	7 (8)	1.0 (0.3 to 2.9)	0.98
Stomach discomfort	17 (20)	16 (19)	1.1 (0.5 to 2.3)	0.88
Loss of appetite or bad taste	27 (31)	21 (25)	1.4 (0.7 to 2.7)	0.33
Lethargy	21 (24)	20 (24)	1.1 (0.5 to 2.1)	0.89
Dizziness	16 (19)	19 (22)	0.8 (0.4 to 1.7)	0.54
Irritability or anxiety	15 (17)	14 (16)	1.1 (0.5 to 2.4)	0.87
Took antiemetic or PPI for symptoms	11 (13)	13 (15)	0.8 (0.3 to 1.9)	0.64
Oral sores	6 (7)	3 (4)	2.1 (0.5 to 8.5)	0.31
Nausea on merely thinking about MTX	4 (5)	4 (5)	1.0 (0.2 to 4.1)	0.99
Hair fall	26 (30)	27 (32)	0.9 (0.5 to 1.8)	0.83
Symptomatic AE by category				
GI†	43 (50)	33 (39)	1.6 (0.9 to 2.9)	0.14
CNS‡	27 (31)	28 (33)	0.9 (0.5 to 1.8)	0.83
Laboratory AE				
Any laboratory AE§	11 (13)	10 (12)	1.1 (0.4 to 2.8)	0.84
WBC<4 x 10^9/L	3 (4)	2 (2)	1.5 (0.2 to 9.1)	1.0
Platelet <100 x 10^9/L	2 (2)	2 (2)	1.0 (0.1 to 7.1)	1.0
AST or ALT >2X ULN	7 (8)	6 (7)	1.2 (0.4 to 3.6)	1.0
AST or ALT >ULN	39 (46)	36 (43)	1.1 (0.6 to 2.1)	0.69

*Includes occurrence of either nausea, vomiting, stomach discomfort, loss of appetite, bad taste, lethargy, dizziness, irritability, anxiety, oral ulcers or alopecia.
†Includes occurrence of either nausea, vomiting, stomach discomfort, loss of appetite or bad taste.
‡Includes occurrence of either lethargy, dizziness, irritability or anxiety.
§Includes leucopaenia (WBC<4 x 10^9/L), thrombocytopaenia (platelet <100 x 10^9/L) or transaminitis (AST or ALT >2X ULN).
AE, Adverse effect; CNS, central nervous system; GI, gastrointestinal; MTX, methotrexate; ULN, Upper limit of normal; WBC, white blood cell count.

at 8 or 16 weeks (online supplemental table S10). Representative chromatograms are shown in online supplemental figure S1.

DISCUSSION

This study did not find any significant difference in efficacy, safety or tolerability between patients on fast escalation (5 mg every 2 weeks) of MTX compared with usual escalation (5 mg every 4 weeks) at 16 weeks (or at the extended efficacy time point of 24 weeks by DAS28-ESR).

In the fast and usual escalation groups, the maximum dose of MTX (25 mg) was reached by 5 and 9 weeks, respectively, such that both groups received 8–12 weeks of full dose before assessment of primary outcome and 16–20 weeks of full dose before the extended efficacy outcome (24 weeks). No significant intergroup difference was observed consistently across a variety of efficacy outcomes at 16 weeks. It may be argued that some differences may emerge on longer follow-up, but even at 24 weeks, we did not find any significant difference in DAS28-ESR between the two groups. Although, the difference of 4 weeks in reaching maximum dose of MTX between the groups may seem minor, it must be placed in context that we wanted to compare the escalation strategies recommended by the 3E initiative (escalation by 5 mg every 2 or 4 weeks) and indirectly, the EULAR guidelines (escalation within 4–6 weeks to optimal dose of 20–25 mg).[1 6] Since most guidelines suggest a time period of 4–6 months for MTX monotherapy to act before stepping-up, exploring strategies to enable a longer exposure to the maximum dose of MTX (25 mg) become imperative. This is particularly relevant in the real-world clinic situation, where a tendency for early step-up to other drugs (including biologics) as early as 4–12 weeks after starting MTX is not uncommon.[5]

The lack of any difference in efficacy was consistent with the finding of similar levels of RBC MTX polyglutamates (1–3) in the two groups at both 8 and 16 weeks. It has been shown previously that longer exposure to higher doses of MTX may lead to selective redistribution towards longer chain MTX polyglutamates (3 to 5), which we could not evaluate in our study.[17] Also, the slow pace of intracellular polyglutamates accumulation, by itself, may be the limiting factor in the rapidity of MTX response achieved. Although Dalrymple *et al* found a median half-life of accumulation of 8 weeks with 90% of maximum steady state levels being reached by 27.5 weeks, they opined that rapid MTX dose escalation from the outset could avoid these delays in achieving steady state levels.[18] Another study by Dervieux *et al* found steady state concentrations to be achieved much earlier, by 7 weeks, being influenced by the MTX dosing intensity.[17]

Previously there are limited studies comparing different escalation strategies of MTX. Data from the initial MTX monotherapy phase of the 'Computer-Assisted Management in Early Rheumatoid Arthritis' (CAMERA) study suggested a better response in the intensive (5 mg/4 weeks) compared with conventional (5 mg/12 weeks) group.[19] Another small prospective study found a trend to better response at 2 months with rapid (5 mg/2 weeks) compared with standard escalation (2.5 mg/6 weeks) of MTX.[20] However, in both these studies, the starting dose of MTX was only 5–7.5 mg, and the escalation of MTX in the comparator (standard) group was very slow. Thus, these are difficult to compare with our study in which all patients were started on 15 mg per week of MTX and relatively fast escalation was used in both groups.

A fear with faster escalation of MTX has been toxicity and intolerance.[21] However, our study did not find any increase in serious AE, infections, cytopaenias or transaminitis when MTX was escalated quickly. Faster escalation did lead to a higher GI intolerance in the initial 8 weeks, which seemed to be dose related, since the difference was not maintained over 16 weeks. Importantly, this was mild and did not translate into an increase in the rates of drug discontinuation or dose reduction, although it may have an impact on continuation in the clinic. These results are consistent with a previous RCT from our centre that showed more nausea with higher starting doses of MTX.[22] Occurrence of oral ulcers was also numerically higher in the fast escalation group.

In this study, we did not check clinical responses prior to MTX escalation-dose escalation was carried out in every patient (unless there were laboratory abnormalities). This was premised

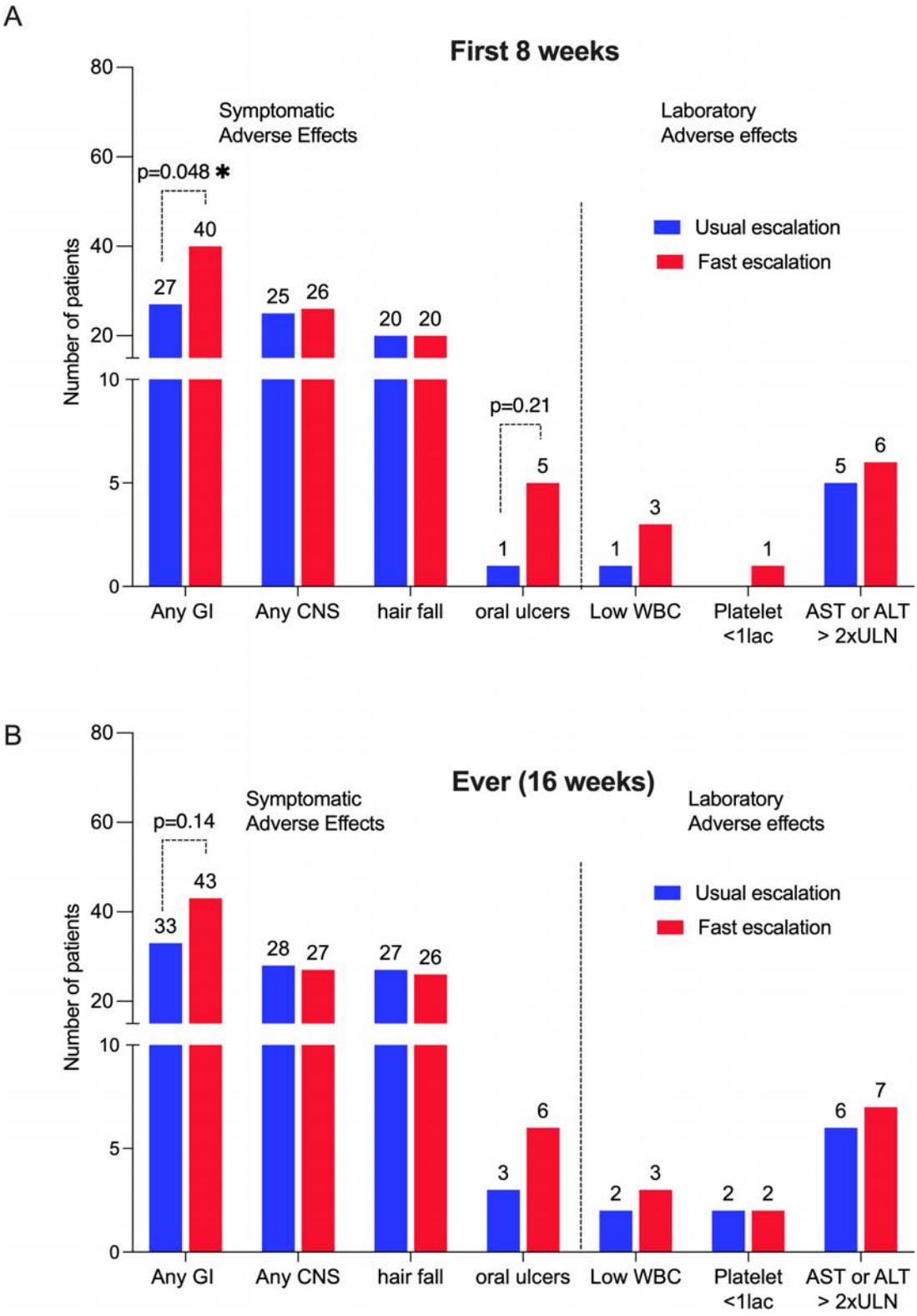


Figure 3 Major symptomatic and laboratory adverse effects in the usual and fast methotrexate escalation groups in the initial 8 weeks (A) and throughout the 16 weeks of the study (B). CNS, central nervous system; GI, gastrointestinal; WBC, white blood cell count. * p<0.05

on our expectation that only a few cases would achieve remission by the end of 2, 4 or 8 weeks (time points of dose escalation). This was exemplified by DAS28-based remission rates of only 4.5% and 7.9% in the usual and fast groups at 8 weeks. We acknowledge that this design might have led to overtreatment in a minority (5%) of patients; however, we felt it was justified as MTX could be de-escalated later in these patients, if they maintained sustained remission.

The occurrence of good EULAR response in 22%–28% and DAS28 LDA or remission in 27%–29% at 16 weeks in our study is consistent with monotherapy arms of larger studies like the Swedish Farmacotherapy (SWEFOT) where 30% patients

achieved LDA at 3–4 months, and step-up arms of the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR), in which LDA was achieved by 28% patients at 6 months.[3 7] Only 10% of patients in our study were on low-dose prednisolone, similar to SWEFOT. Although, this does hamper generalisability, as low-dose glucocorticoids are often added in the initial 3–6 months in the clinic, but at the same time, it exemplifies that optimally dosed MTX by itself can be very effective. We avoided them to prevent masking of any inter-group differences, but allowed one dose of intramuscular or intraarticular methylprednisolone 80 mg.

The major limitation of our study was that we only included patients who were 55 years and younger in age, thus the results cannot be generalised to older patients. We excluded older individuals as we generally start them on a lower dose (7.5–10 mg) of MTX, due to their higher risk of AE. It is noteworthy that the population in India is mostly young (only 8% above 60 years.[23] Another limitation is that we could not reach the targeted sample size (due to COVID-19) which reduced the power to 80%; also, the study was not powered for comparing the difference in AE between the two groups. As we did not include patient and physician global assessments, simplified disease activity index (SDAI), clinical disease activity index (CDAI) and ACR responses could not be calculated. We used 3-variable DAS-28 as patient global assessment (PtGA) is a difficult concept to understand in our culture, and patients find it easier to comment on change in status (anamnesis).[13] This may be relevant to other countries or populations as well- a recent study from USA reported that PtGA was confusing to 40% of patients, more so in the less educated,[24] and a multinational study found that one-third of near-remission patients rated the PtGA >4.[25] Although patient reported outcomes are important, PtGA (along with fatigue, etc) may form a separate aspect of disease burden, distinct from disease activity.[26] Finally, we may be criticised for not using parenteral MTX or splitting oral MTX, however, they are unlikely to have led to an intergroup difference.

To conclude, MTX remains the gold-standard drug for RA worldwide, being especially crucial for developing countries like India in view of its low cost[27]; thus, it is important to generate evidence to optimise its dosing strategy. The strength of our pragmatic RCT is that we compared two relatively fast escalation strategies recommended by guidelines. The results from this study suggest that 'faster is not always better' in the context of MTX escalation in RA, that is, after starting MTX at a dose of 15 mg per week, a faster MTX escalation of 5 mg every two weeks (compared to four weeks) did not lead to better outcomes at 16–24 weeks.

Acknowledgements MTX was provided free of cost as a gift from IPCA laboratories (Mumbai, Maharashtra, India).

Contributors VDhi, SiJ, SN and AA designed the study. SiJ, VDhi, AA, RG, SN, SM, SKS, AS and SaJ were involved in collecting patients' data and executing the study. BL, AK, SM and VDha performed the laboratory procedures and interpreted them. VDhi and SiJ performed the statistical analyses. VDhi and SiJ drafted the manuscript; AA and RG gave critical inputs. All authors approved the final submitted version of the manuscript.

Funding A Departmental grant (Department of Internal Medicine, Postgraduate Institute of Medical Education and Research) and grants from the Indian Rheumatology Association and Physician Research Foundation (Association of Physicians of India) were used to fund the laboratory assays used in the study.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the Institutional Ethics Committees of all study centres: Postgraduate Institute of Medical Education and Research, Chandigarh (INT/IEC/2018/001406); All India Institute of Medical Sciences, New Delhi (IEC/673); and Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow (2018-178-CP-107).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

ORCID iDs
Varun Dhir http://orcid.org/0000-0002-3626-0694
Shankar Naidu http://orcid.org/0000-0002-9727-044X

REFERENCES

1 Smolen JS, Landewé RBM, Bijlsma JWJ, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;79:685–99.
2 Singh JA, Saag KG, Bridges SL, *et al*. 2015 American College of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2016;68:1–26.
3 O'Dell JR, Curtis JR, Mikuls TR, *et al*. Validation of the methotrexate-first strategy in patients with early, poor-prognosis rheumatoid arthritis: results from a two-year randomized, double-blind trial. *Arthritis Rheum* 2013;65:1985–94.
4 Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, *et al*. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007;146:406–15.
5 Rohr MK, Mikuls TR, Cohen SB, *et al*. Underuse of methotrexate in the treatment of rheumatoid arthritis: a national analysis of prescribing practices in the US. *Arthritis Care Res* 2017;69:794–800.
6 Visser K, Katchamart W, Loza E, *et al*. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E initiative. *Ann Rheum Dis* 2009;68:1086–93.
7 van Vollenhoven RF, Ernestam S, Geborek P, *et al*. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. *Lancet* 2009;374:459–66.
8 Emery P, Horton S, Dumitru RB, *et al*. Pragmatic randomised controlled trial of very early etanercept and MTX versus MTX with delayed etanercept in RA: the VEDERA trial. *Ann Rheum Dis* 2020;79:464–71.
9 Aletaha D, Neogi T, Silman AJ, *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League against rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580–8.
10 Fransen J, van Riel PLCM. The disease activity score and the EULAR response criteria. *Clin Exp Rheumatol* 2005;23:S93–9.
11 Sandhu A, Dhir V, Bhatnagar A, *et al*. High methotrexate triglutamate level is an independent predictor of adverse effects in Asian Indian rheumatoid arthritis Patients-A preliminary study. *Ther Drug Monit* 2017;39:157–63.
12 Fransen J, van Riel PLCM. The disease activity score and the EULAR response criteria. *Rheum Dis Clin North Am* 2009;35:745–57.
13 Malaviya A. Outcome measures in rheumatoid arthritis – Indian perspective. *Indian J Rheumatol* 2013;8:S36–7.
14 Kumar A, Malaviya AN, Pandhi A, *et al*. Validation of an Indian version of the health assessment questionnaire in patients with rheumatoid arthritis. *Rheumatology* 2002;41:1457–9.
15 Gupta D, Biswas D, Kabiraj P. COVID-19 outbreak and urban dynamics: regional variations in India. *GeoJournal* 2021:1–19.
16 Faul F, Erdfelder E, Buchner A, *et al*. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods* 2009;41:1149–60.
17 Dervieux T, Zablocki R, Kremer J. Red blood cell methotrexate polyglutamates emerge as a function of dosage intensity and route of administration during pulse methotrexate therapy in rheumatoid arthritis. *Rheumatology* 2010;49:2337–45.
18 Dalrymple JM, Stamp LK, O'Donnell JL, *et al*. Pharmacokinetics of oral methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2008;58:3299–308.
19 Verstappen SMM, Jacobs JWG, van der Veen MJ, *et al*. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. computer assisted management in early rheumatoid arthritis (camera, an open-label strategy trial). *Ann Rheum Dis* 2007;66:1443–9.
20 Jassim I, Ali H, Al-Allaf A. Methotrexate in rheumatoid arthritis, starting dose and dose escalation regimens. *Ann Rheum Dis* 2007;66:S440–1.

21 Taylor PC, Balsa Criado A, Mongey A-B, *et al*. How to Get the Most from Methotrexate (MTX) Treatment for Your Rheumatoid Arthritis Patient?-MTX in the Treat-to-Target Strategy. *J Clin Med* 2019;8. doi:10.3390/jcm8040515. [Epub ahead of print: 15 04 2019].
22 Dhir V, Singla M, Gupta N, *et al*. Randomized controlled trial comparing 2 different starting doses of methotrexate in rheumatoid arthritis. *Clin Ther* 2014;36:1005–15.
23 Census of India. Available: https://censusindia.gov.in/vital_statistics/SRS_Report/9Chap%202%20-%202011.pdf [Accessed 2 May 2021].
24 Hirsh J, Wood P, Keniston A, *et al*. Limited health literacy and patient confusion about rheumatoid arthritis patient global assessments and model disease states. *Arthritis Care Res* 2019;71:611–9.
25 Ferreira RJO, Carvalho PD, Ndosi M, *et al*. Impact of patient's global assessment on achieving remission in patients with rheumatoid arthritis: a multinational study using the Meteor database. *Arthritis Care Res* 2019;71:1317–25.
26 Pazmino S, Lovik A, Boonen A, *et al*. Does including pain, fatigue, and physical function when assessing patients with early rheumatoid arthritis provide a comprehensive picture of disease burden? *J Rheumatol* 2021;48:174–8.
27 Handa R. Rheumatology in India--quo vadis? *Nat Rev Rheumatol* 2015;11:183–8.

CLINICAL SCIENCE

Investigating changes in disease activity as a mediator of cardiovascular risk reduction with methotrexate use in rheumatoid arthritis

Tate M Johnson ,[1,2] Harlan R Sayles,[1,3] Joshua F Baker,[4,5] Michael D George,[4,5] Punyasha Roul,[1] Cheng Zheng,[3] Brian Sauer,[6,7] Katherine P Liao,[8] Daniel R Anderson,[9] Ted R Mikuls ,[1,2] Bryant R England [1,2]

Handling editor Josef S Smolen

► Additional online supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220125).

For numbered affiliations see end of article.

Correspondence to
Dr Bryant R England, Medicine & Research Service, VA Nebraska-Western Iowa Health Care System, Omaha, Nebraska, USA;
bryant.england@unmc.edu

Received 8 February 2021
Accepted 19 May 2021
Published Online First 28 May 2021

ABSTRACT

Objective Examine the association of methotrexate (MTX) use with cardiovascular disease (CVD) in rheumatoid arthritis (RA) using marginal structural models (MSM) and determine if CVD risk is mediated through modification of disease activity.

Methods We identified incident CVD events (coronary artery disease (CAD), stroke, heart failure (HF) hospitalisation, CVD death) within a multicentre, prospective cohort of US Veterans with RA. A 28-joint Disease Activity Score with C-reactive protein (DAS28-CRP) was collected at regular visits and medication exposures were determined by linking to pharmacy dispensing data. MSMs were used to estimate the treatment effect of MTX on risk of incident CVD, accounting for time-varying confounders between receiving MTX and CVD events. A mediation analysis was performed to estimate the indirect effects of methotrexate on CVD risk through modification of RA disease activity.

Results Among 2044 RA patients (90% male, mean age 63.9 years, baseline DAS28-CRP 3.6), there were 378 incident CVD events. Using MSM, MTX use was associated with a 24% reduced risk of composite CVD events (HR 0.76, 95% CI 0.58 to 0.99) including a 57% reduction in HF hospitalisations (HR 0.43, 95% CI 0.24 to 0.77). Individual associations with CAD, stroke and CVD death were not statistically significant. In mediation analyses, there was no evidence of indirect effects of MTX on CVD risk through disease activity modification (HR 1.03, 95% CI 0.80 to 1.32).

Conclusions MTX use in RA was associated with a reduced risk of CVD events, particularly HF-related hospitalisations. These associations were not mediated through reductions in RA disease activity, suggesting alternative MTX-related mechanisms may modify CVD risk in this population.

Key messages

What is already known about this subject?

- Several studies have demonstrated a reduced risk of atherothrombotic cardiovascular disease (CVD) with methotrexate (MTX) use, but its effect on heart failure (HF) and the mechanisms underlying its cardioprotective effect are poorly understood.

What does this study add?

- An evaluation of MTX treatment effect on CVD events, using novel marginal structural models accounting for the effect of time-varying confounders on the propensity to receive MTX, demonstrated a 24% reduction in composite CVD events and a 57% reduction in HF hospitalisation.
- Using mediation analysis, we observed that the effects of MTX use on CVD risk reduction are not mediated by reduction in rheumatoid arthritis (RA) disease activity.

How might this impact on clinical practice or future developments?

- These preliminary findings suggest that MTX-related mechanisms other than disease activity control may provide CVD, and particularly HF, benefit in patients with RA.

INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of death in rheumatoid arthritis (RA)[1 2] owed largely to a heightened risk of coronary artery disease (CAD), stroke and heart failure (HF)[3–5] only partially explained by traditional CVD risk factors.[6] Controlling RA disease activity and select disease-modifying antirheumatic drugs (DMARDs) are speculated to provide cardioprotective benefits. Though methotrexate (MTX) did not reduce risk in non-RA patients with established CVD in the absence of systemic inflammation,[7] multiple observational studies have demonstrated benefit in patients with RA. MTX was associated with a 28% lower risk of CVD events in a meta-analysis of observational studies including over 200 000 patients with RA.[8] Recent cohort studies report 20%–60% reductions in CVD events with MTX treatment.[9–11] While associations with atherothrombotic CVD is more extensively studied, MTX has also been associated with a reduced risk of HF.[12 13]

The mechanisms by which MTX reduces CVD in RA remain poorly understood. Indirectly, MTX may lower CVD risk by reducing RA disease activity. Potential direct cardioprotective mechanisms of MTX include increased cholesterol efflux capacity, improved endothelial function, reduced foam cell generation and the ability to scavenge free radicals

To cite: Johnson TM, Sayles HR, Baker JF, *et al*. *Ann Rheum Dis* 2021;**80**:1385–1392.

implicated in CVD pathogenesis.[14–17] Improved understanding of the mechanisms by which MTX reduces CVD in RA may help clinicians optimally use MTX as therapeutic options expand.

In this study, we evaluated the association of MTX with incident CVD in a prospective cohort of US Veterans with RA to test the hypothesis that CVD risk reduction with MTX in RA is mediated through modification of RA disease activity.

PATIENTS AND METHODS

Study design

We conducted a cohort study in the Veterans Affairs Rheumatoid Arthritis (VARA) registry, a multicentre, prospective cohort of US Veterans with RA initiated in 2003.[18] Participants are >18 years of age and satisfy 1987 American College of Rheumatology (ACR) classification criteria for RA.[19] Participants signed informed consent for participation. Demographic data are obtained at enrolment while clinical data, including ACR Core Measures for RA disease activity, are collected at each visit. We followed patients from the latter of VARA enrolment or 1 April 2005 until incident CVD event, death or end of study period (1 April 2015).

DMARD exposure

Prescription fills for MTX and other conventional DMARDs (hydroxychloroquine, sulfasalazine, leflunomide), tumour necrosis factor (TNF) inhibitors (adalimumab, etanercept, infliximab, certolizumab, golimumab), non-TNF biologics (rituximab, abatacept, tocilizumab) and prednisone were identified from pharmacy dispensing records in the VA Corporate Data Warehouse (CDW).[20] Drug courses were defined from dispensing data using established algorithms.[21] Because our hypothesis focused on whether current disease activity (affected by prior MTX exposure) mediated future CVD risk, we used a 90-day lookback (180 days for rituximab) at each encounter to define drug exposure (online supplemental figure 1).

RA disease activity

Patient and provider global assessments of disease activity, swollen and tender joint counts, and C reactive protein (CRP) values were used to calculate time-varying 28-joint Disease Activity Scores (DAS28-CRP) at each VARA encounter. Missing disease activity components (joint counts 3.6%, global assessment 10.8% and acute phase reactant 5.1% of observations) were imputed using the last observation carried forward for subsequent missing data.

Covariates

Covariates were selected a priori and included age, sex, race, body mass index (BMI) categories, smoking status, comorbidities (including the Rheumatic Disease Comorbidity Index[22]), and use of aspirin, statins and non-steroidal anti-inflammatory drugs (NSAIDs). Demographics and smoking status were obtained at baseline. Time-varying BMI was obtained from the VA CDW, using the value closest to the visit date.[23] Comorbidities including hypertension, hyperlipidaemia, diabetes, CAD, cerebrovascular disease, HF, chronic kidney disease and chronic liver disease were defined by ≥2 inpatient or outpatient International Classification of Disease, Ninth Revision (ICD-9) codes prior to the index date (online supplemental table 1). Statin use was defined at baseline by the presence of at least one dispensing episode in the year prior to index. Aspirin and NSAIDs were defined at each visit using registry data as these agents are frequently obtained over the counter.

Outcomes

The primary outcome was a composite of incident (occurring after the index date) CAD (myocardial infarction (MI), percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)), stroke, HF hospitalisation or CVD-related death. Secondary outcomes included a composite of atherothrombotic major adverse cardiovascular events (MACE; CAD, stroke or CVD-related death) and individual CVD outcomes. CVD-related deaths were determined from the National Death Index (NDI), using ICD-10 codes I00–I99. Non-fatal events were identified using an administrative algorithm incorporating previously validated ICD-9 codes (online supplemental table 2).[24–30] We queried the VA CDW, requiring a primary or secondary hospital discharge diagnosis for CAD or stroke, including transient ischaemic attack. Since it is a chronic condition, HF was required to be a primary discharge diagnosis. Coronary revascularisation was identified using ICD-Procedure and Current Procedural Terminology codes for PCI and CABG. A random sample of CVD events was validated by medical record review using previously described adjudication criteria,[24 26] yielding a positive predictive value (PPV) of 90% for CAD and 83% for HF hospitalisations. The PPV for stroke was 70%; thus, all stroke events were validated by medical record review. Since acute events such as MI and stroke may result in treatment outside the VA, we identified outpatient CAD and stroke diagnoses in patients without a hospitalised event in the VA (online supplemental table 2). All events identified through this approach were validated by medical record review.

Statistical analysis

Baseline characteristics were stratified by ever-exposure or never-exposure to MTX during the study period. Crude incidence rates (IRs) and IR ratios (IRRs) for CVD events were estimated based on time-varying MTX exposure.

Marginal structural models (MSM) were used to evaluate the association of time-varying MTX use with CVD events. As time-varying covariates may dynamically affect the likelihood of receiving MTX, traditional analytical methods assessing the association of MTX with CVD events are at risk for substantial residual confounding.[31] MSM uses inverse probability weighting to account for the influence of time-fixed and time-varying confounders on the propensity to receive MTX, providing a more robust measure of causality between MTX and incident CVD risk.[31] MSM methods are described in detail in online supplemental appendix, following the approach described by Fewell *et al*.[32] Variables from current and prior visits were used to estimate the propensity to receive MTX at the current visit. Standardised mean differences (SMD) were calculated to ensure covariate balance.[33] In secondary analyses, we stratified patients by baseline DAS28-CRP (moderate/high vs remission/low) and high-sensitivity CRP (hs-CRP, with a previously used cut-off of 2 mg/L[34]), restricted analyses to those without a history of MACE or HF, and examined these associations in those with RA duration of <5 years.

Recognising that RA disease activity represents a potential confounder and/or mediator in the exposure–outcome pathway between MTX and CVD (figure 1), additional MSMs were used to estimate natural indirect effects through disease activity modification and direct effects of MTX exposure on CVD risk based on this causal structure.[35] Specific methods for this approach are detailed in online supplemental appendix. DAS28-CRP at the current visit served as the mediator between treatment with MTX and subsequent CVD events. Secondary analyses

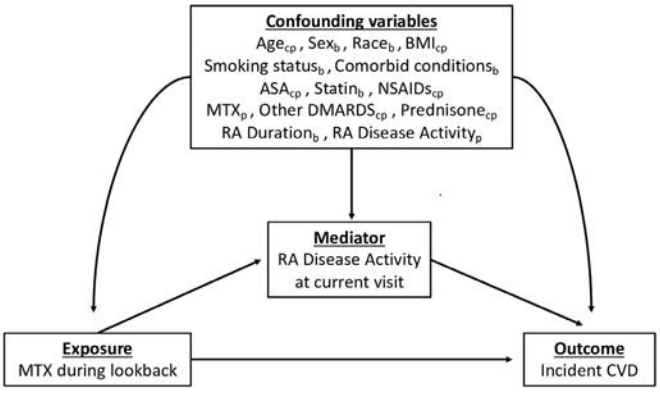


Figure 1 Directed acyclic graph modelling the causal framework between methotrexate (exposure) and incident cardiovascular disease (outcome). RA disease activity is both affected by MTX exposure and influences CVD risk, thus acts as the primary mediator of interest in this analysis. All confounding variables listed are assumed to influence the exposure, mediator and CVD outcome. RA disease activity measures included the DAS28-CRP as well as measures of systemic inflammation (erythrocyte sedimentation rate and CRP). ASA, aspirin; BMI, body mass index; CRP, C reactive protein; CVD, cardiovascular disease; DMARDs, disease modifying anti-rheumatic drugs; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis.

examined measures of systemic inflammation (erythrocyte sedimentation rate or CRP) as mediators between MTX exposure and CVD events. All analyses were completed using Stata V.15.1 software (StataCorp) within the VA Informatics and Computing Infrastructure.[20]

Patient and public involvement

Patients and the public were not directly involved in the design or completion of this study.

RESULTS

Baseline characteristics

We followed 2044 Veterans with RA over 10 360 patient-years (median follow-up of 4.9 years, mean of 11.4 visits per patient). Patients were predominantly male (90.0%), white (77.0%), in their seventh decade (mean age 63.9 years) and seropositive (79.2% rheumatoid factor (RF) positive, 77.8% anti-cyclic citrullinated peptide (anti-CCP) positive) with a mean DAS28-CRP of 3.6. Of 1090 patients on MTX at baseline, 561 discontinued MTX during the follow-up. Among patients not on MTX at baseline, 272 patients initiated MTX during the follow-up. Follow-up time was similar between patients treated with (5.0 years) or without (4.8 years) MTX at baseline. Demographics, BMI, smoking status and CVD-related comorbidities were similar by exposure group, with a modestly higher frequency of hyperlipidaemia in the MTX ever-exposed population (table 1). Chronic kidney disease and liver disease were more common in MTX unexposed patients, as was the use of leflunomide and sulfasalazine. Across all observations, biological DMARD and prednisone use was similar between MTX exposure groups, while other conventional DMARDs were more frequent in MTX unexposed patients (52.8% vs 36.9% of observations).

Table 1 Baseline characteristics of veterans with rheumatoid arthritis, stratified by methotrexate (MTX) ever-exposure (N=2044)

	MTX ever-exposed (N=1369)	MTX never-exposed (N=675)
Age (years)	63.8 (11.2)	64.1 (10.6)
Male sex, N (%)	1238 (90.4)	602 (89.2)
White race, N (%)	1046 (76.4)	527 (78.1)
BMI (kg/m^2)	28.7 (5.8)	28.1 (5.3)
Healthcare utilisation*		
Inpatient	0.2 (0.6)	0.2 (0.7)
Outpatient	16.8 (15.0)	17.8 (16.2)
High school graduate, N (%)	1116 (86.6)	536 (86.7)
Smoking status, N (%)		
Current	348 (25.5)	189 (28.1)
Former	719 (52.7)	363 (54.0)
Never	298 (21.8)	120 (17.9)
Comorbid conditions, N (%)		
RDCI	1.29 (1.31)	1.40 (1.39)
Hypertension	858 (62.7)	436 (64.6)
Hyperlipidaemia	682 (49.8)	315 (46.7)
Diabetes	301 (22.0)	154 (22.8)
Coronary artery disease	327 (23.9)	173 (25.6)
Cerebrovascular disease	91 (6.6)	53 (7.9)
Heart failure	109 (8.0)	63 (9.3)
Chronic kidney disease	66 (4.8)	55 (7.5)
Chronic liver disease	22 (1.6)	60 (8.9)
Lung disease	303 (22.1)	204 (30.2)
RA-related factors		
Rheumatoid factor positive, N (%)	1035 (78.2)	520 (81.1)
Anti-CCP positive, N (%)	1013 (76.7)	513 (80.2)
RA disease duration (years)	10.5 (11.1)	13.4 (11.6)
Tender joint count	5.5 (6.9)	4.3 (6.2)
Swollen joint count	4.5 (5.6)	3.6 (5.0)
Patient Global	41.2 (25.7)	39.5 (24.7)
Provider Global	35.0 (23.1)	32.9 (22.6)
ESR (mm/hr)	25.6 (22.6)	28.3 (24.4)
CRP (mg/dL)	1.5 (2.4)	1.6 (2.6)
hs-CRP (mg/L)	1.2 (2.0)	1.2 (1.9)
DAS28-CRP	3.7 (1.4)	3.4 (1.3)
MDHAQ	0.9 (0.6)	0.9 (0.6)
Medication use, N (%)		
Hydroxychloroquine	306 (25.9)	175 (22.4)
Sulfasalazine	106 (7.7)	92 (13.6)
Leflunomide	52 (3.8)	144 (21.3)
Prednisone	605 (44.2)	252 (37.3)
TNF inhibitor	343 (25.1)	210 (31.1)
Non-TNF biologic	23 (1.7)	15 (2.2)
Statins	599 (43.8)	290 (43.0)
Aspirin	85 (6.2)	41 (6.1)
NSAIDs	475 (34.7)	234 (34.7)

Baseline characteristics are stratified by whether a patient was ever exposed to MTX during the study period. Values mean (SD) unless otherwise noted.
*Number of visits in the 12 months prior to index date.
.BMI, body mass index; DAS28, disease activity score with 28-joint count; ESR, erythrocyte sedimentation rate; hs-CRP, high sensitivity C-reactive protein; MDHAQ, multidimensional health assessment questionnaire; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; RDCI, Rheumatic Disease Comorbidity Index.

Incidence of CVD events

We identified 378 composite CVD events with an incidence of CAD, stroke, HF hospitalisation and CVD-related death of 14.2, 6.0, 7.9 and 15.0 events per 1000 person-years, respectively (table 2). Crude IRRs demonstrated a reduced incidence of HF hospitalisation (IRR 0.48, 95% CI 0.30 to 0.77) as well as composite CVD events (IRR 0.83, 95% CI 0.67 to 1.02) and CVD-related death (IRR 0.76, 95% CI 0.55 to 1.05) in MTX

Table 2 Incidence rates of cardiovascular events in veterans with rheumatoid arthritis (per 1000 person-years)

Event category*	N	Follow-up time (PY)	Mean time to event, years	Incidence rates (per 1000 PY)		IRR (95% CI)
				MTX ever-exposed	MTX never-exposed	
Composite	378	10 360	3.42	33.05	39.88	0.83 (0.67 to 1.02)
HF hospitalisation	87	10 956	3.47	5.17	10.66	**0.48 (0.30 to 0.77)**
MACE	342	10 443	3.45	30.32	35.14	0.86 (0.69 to 1.07)
CAD	151	10 605	3.08	13.50	14.97	0.90 (0.65 to 1.26)
Stroke	66	10 934	3.36	6.13	5.95	1.03 (0.62 to 1.72)
CVD Death	167	11 098	3.99	13.00	17.03	0.76 (0.55 to 1.05)

Values listed in bold indicate p<0.05.
*MACE is a composite of outcomes included in CAD, stroke and CVD death. CAD includes acute myocardial infarction, percutaneous coronary intervention or coronary artery bypass.
.CAD, coronary artery disease; CVD, cardiovascular disease; HF, heart failure; IRR, incidence rate ratio; MACE, major adverse cardiovascular event; MTX, methotrexate; PY, person years; RA, rheumatoid arthritis.

exposed patients in unadjusted analyses, although the latter two were not statistically significant. IRRs for MACE, CAD and stroke were not significantly different between MTX exposed and unexposed patients (table 2).

Mtx and CVD risk using MSM

In MSM including time-varying variables from the current and prior encounter, covariate balance was achieved between exposure groups (SMD <0.1 for all variables). MTX was associated with a reduced risk of composite CVD events (HR 0.76, 95% CI 0.58 to 0.99) and HF-related hospitalisation (HR 0.43, 95% CI 0.24 to 0.77). While MTX was associated with a numeric reduction in MACE (HR 0.82, 95% CI 0.63 to 1.06), CAD (HR 0.84, 95% CI 0.55 to 1.28), stroke (HR 0.72, 95% CI 0.34 to 1.53) and CVD-related death (HR 0.78, 95% CI 0.55 to 1.13), these differences were not statistically significant (table 3).

When stratified by baseline DAS28-CRP, associations between MTX and composite CVD events and MACE were generally numerically stronger among those with moderate to high DAS28-CRP at baseline, though 95% CIs were overlapping (online supplemental table 3). Minimal differential associations between MTX and CVD events were observed based on a hs-CRP cut-off of 2 g/dL at baseline (online supplemental table 3). When restricting analyses to those without a history of MACE or HF (online supplemental table 4) as well as RA duration <5 years (online supplemental table 5), similar estimates were observed, although this did not reach statistical significance for HF (HR 0.52, 95% CI 0.23 to 1.18). Sensitivity analysis including education, lung disease, and baseline MDHAQ were similar, but less precise (composite HR 0.79, 95% CI 0.59 to 1.05, HF hospitalisation 0.45, 95% CI 0.24 to 0.84) (online supplemental table 6).

Table 3 Association of methotrexate use with cardiovascular disease events in veterans with rheumatoid arthritis*

Event category†	HR (95% CI)	P value
Composite	**0.76 (0.58 to 0.99)**	**0.04**
HF hospitalisation	**0.43 (0.24 to 0.77)**	**0.005**
MACE	0.82 (0.63 to 1.06)	0.12
CAD	0.84 (0.55 to 1.28)	0.42
Stroke	0.72 (0.34 to 1.53)	0.39
CVD Death	0.79 (0.55 to 1.13)	0.19

Values listed in bold indicate p<0.05.
*Marginal structural models adjusting for time-varying age, BMI, RA disease activity, and medication use (prednisone, conventional and biological DMARDs, ASA and NSAIDs). Time-invariant variables assessed at baseline included sex, race, smoking status, RA duration, comorbidities and statin use. Primary analysis includes variables from the current and prior visit into the propensity to receive MTX.
†MACE is a composite of CAD, stroke and CVD death. CAD includes acute myocardial infarction, percutaneous coronary intervention or coronary artery bypass.
.ASA, aspirin; BMI, body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; DMARD, disease-modifying anti-rheumatic drug; HF, heart failure; MACE, major adverse cardiovascular event; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis.

Mediation analysis of MTX and CVD risk

In mediation analyses modelling RA disease activity as the primary mediator between MTX exposure and CVD events, indirect effects of MTX on CVD events through modification of RA disease activity were not significant (range HR 0.87–1.06, all ps>0.05, figure 2). Direct effects of MTX were associated with a lower risk of HF hospitalisation (HR 0.41, 95% CI 0.18 to 0.92) and a numeric, but non-significant, reduction in composite CVD events (HR 0.74, 95% CI 0.51 to 1.07). Similarly, secondary analyses did not demonstrate that reductions in inflammatory markers mediated MTX-related CVD risk (range HR 0.91–1.48, figure 3).

DISCUSSION

In this multicentre, prospective cohort of US Veterans with RA, we observed a significantly reduced risk of CVD events associated with MTX use, independent of age, BMI, traditional CVD risk factors, RA disease activity and other RA therapies using state-of-the-art causal inference techniques. To our knowledge, this is among the first studies to demonstrate a greater risk reduction for HF hospitalisations with MTX use compared with CAD and stroke, supporting a potential cardioprotective role of MTX extending beyond atherothrombotic events. While the association of MTX with lower CVD risk in RA has been consistently reported,[3 4 6] whether this is driven primarily by reductions in RA disease activity has not been elucidated. Through mediation analysis, we observed that the cardioprotective effect of MTX was not attributable to modification of disease activity. This suggests that use of MTX may have additional direct cardiovascular benefits in patients with RA that are independent of its role in controlling clinical RA disease activity, though this requires further study.

We estimated that MTX exposed patients carried a 24% lower risk of CVD, similar to prior studies supporting a cardioprotective effect of MTX.[8 36] Non-significant trends suggesting a protective effect against MACE (HR 0.82, 95% CI 0.63 to 1.06) or the MACE components of CAD (HR 0.84, 95% CI 0.55 to 1.28) and stroke (HR 0.72, 95% CI 0.34 to 1.53) are similar

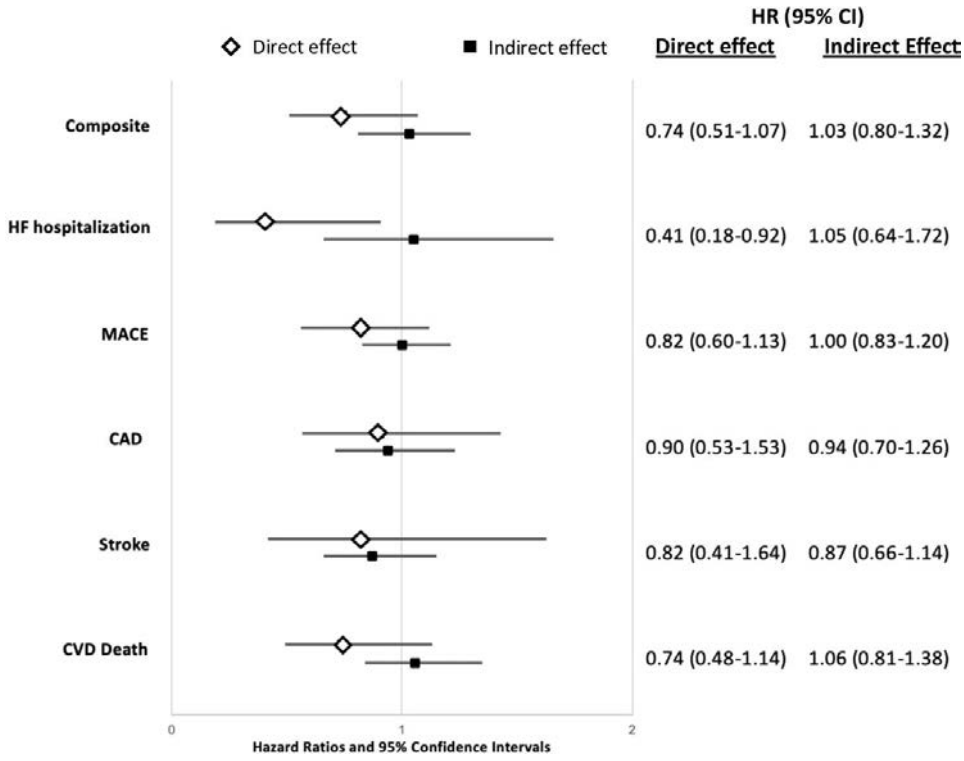


Figure 2 Forest plot illustrating the natural direct and natural indirect effects of MTX mediated by DAS28-CRP with CVD events using a counterfactual-based mediation analysis abbreviations: CAD, coronary artery disease; CVD, cardiovascular disease; DAS, Disease Activity Score; HF, heart failure; MACE, major adverse cardiovascular event; MTX, methotrexate.

to prior estimates.[8 36] While most prior studies use covariate adjustment in proportional hazards regression models, their adjustment for time-varying covariates that confound MTX use is limited. We used MSM, an approach that more accurately accounts for time-varying variables that influence the propensity to receive MTX and develop CVD events.[31] Importantly, this represents a novel methodological approach in addressing this high-impact clinical question.

Patients with RA are at a 20%–50% increased risk of HF referent to the general population, independent of ischaemic heart disease and suffer higher mortality rates after HF diagnosis.[5 37–42] Given the chronic nature of HF often complicated by recurrent hospitalisations, poorly controlled HF poses a substantial burden to patients and healthcare systems.[43] Effective prevention and management of HF in patients with RA could yield considerable benefits in this population. Initial case–control and cohort studies in RA demonstrated a 20%–50% reduction in HF risk associated with MTX use.[12 13 37] Our study builds on these findings, demonstrating a 57% lower risk of HF hospitalisation in those with MTX exposure in a large, multicentre, prospective RA cohort while accounting for longitudinal RA disease activity and other DMARD use. When restricting to those without HF at enrolment, a similar, but less precise, reduction in new-onset HF was seen (online supplemental table 4).

Mechanisms underpinning CVD risk in RA are multifactorial, including traditional CVD risk factors, RA disease activity, systemic inflammation, lipoprotein dysfunction, endothelial dysfunction and oxidative stress.[44] We demonstrated that indirect effects of MTX through modification of RA disease activity and systemic inflammation did not mediate CVD risk reduction in this cohort. Our findings suggest potential benefit of MTX in the context of CVD risk management beyond its important role of improving disease activity, particularly as it relates to reducing HF hospitalisations. Supporting this, a previous study of patients initiating biological DMARDs demonstrated a 24% lower risk of incident CVD in those on concomitant MTX.[45] Continued research is warranted to elucidate direct effects of MTX, such as improvements in lipoprotein and endothelial function,[14–17] on CVD outcomes in RA. Although not observed as an indirect effect from MTX in this study, evidence linking disease activity with CVD risk necessitates tight control of RA for lowering CVD risk.

The effect of antirheumatic drugs on CVD risk in non-RA patients is of increasing interest.[34 46] Whether MTX-related mechanisms might translate to effective CVD prevention outside of RA was investigated in the Cardiovascular Inflammation Reduction Trial.[7] In non-RA patients with prior CAD, low-dose MTX treatment did not reduce CVD events compared with placebo. These findings may relate to the inclusion of patients without high levels of systemic inflammation,[7] though in our study baseline hs-CRP minimally influenced the association between MTX and CVD events. RA likely portends a more complex inflammatory milieu than the non-RA population, thus, it remains unclear whether a specific inflammatory phenotype in the non-RA population might receive CVD benefit from MTX.

There are limitations to this study. This is an older, male-predominant cohort of US Veterans, which may limit generalisability of these findings. Sample size did not allow for a new-user, active-comparator design, thus changes in disease activity related to MTX may be underestimated and further study is required to specifically compare the observed CVD benefits of MTX, alone or in combination, with other DMARD regimens. As in any observational study, residual confounding is possible and manifests as a direct effect in mediation analyses, which must be considered when interpreting a causal link between MTX and CVD risk. While longitudinal measures allowed for robust

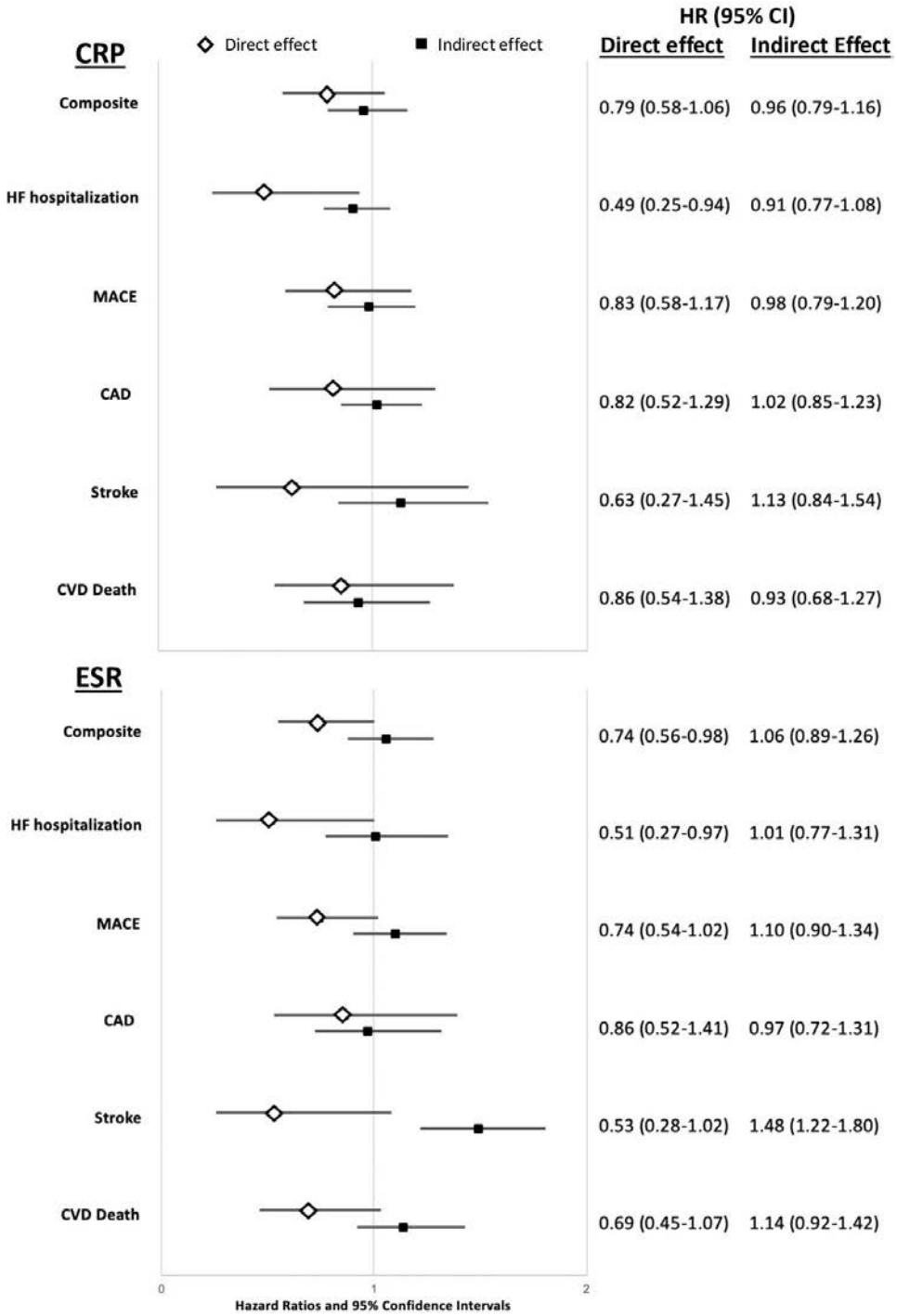


Figure 3 Forest plot illustrating the natural direct and natural indirect effects of MTX with cardiovascular disease events mediated by CRP (A) and ESR (B) using a counterfactual-based mediation analysis. CAD, coronary artery disease; CRP, C reactive protein; CVD, cardiovascular disease; ESR, erythrocyte sedimentation rate; HF, heart failure; MACE, major adverse cardiovascular event; MTX, methotrexate.

assessment of indirect effects of MTX through modification of disease activity, additional studies could explore the contribution of alternative mediators to CVD risk reduction with MTX use, such as reduced glucocorticoid dose. Additionally, folic acid supplementation may lead to modest reductions in atherothrombotic CVD,[47] although this has not been shown to affect HF risk. Though time-varying data were available for many variables, smoking status, statin use and comorbid conditions were available only at baseline. As this is an older population with a high degree of established comorbidity, the new incidence of traditional CVD comorbidities during follow-up has been shown to be relatively infrequent in this cohort.[48] Left truncation of our cohort limits the ability to account for accumulated RA disease activity and DMARD exposure prior to index, though including surrogate measures of prior RA disease activity including RA duration, DMARD (both conventional and biologic) and prednisone exposure, as well as MDHAQ did not substantially affect results. Because we relied on administrative data to identify CVD events, an event outside of the VA may be missed, though efforts were made to systematically minimise outcome misclassification by identifying new outpatient diagnoses and validating events through medical record review.

Causal inference methodology is rapidly evolving, offering means for more robust estimates of treatment effects and disease and/or treatment mechanisms in the observational setting. The use of propensity score-based methods is increasing, particularly in pharmacoepidemiological studies.[49] There remains underutilisation of MSM and causal mediation analyses in longitudinal observational studies of rheumatic diseases. Continued implementation of these methods in epidemiological studies is needed to improve the validity of study findings and to elucidate the mechanisms underlying observed associations.

In conclusion, MTX exposure was associated with a 24% reduced risk of CVD events including a 57% reduced risk of HF hospitalisation in a large RA registry linked to national VA data. These cardioprotective effects were not attributable to indirect effects through modification of RA disease activity or systemic inflammation. These data suggest MTX may offer CVD benefit, particularly in HF, beyond its role in reducing RA disease activity, and these roles should be especially considered in RA patients at high risk of CVD.

Author affiliations
[1]Medicine & Research Service, VA Nebraska-Western Iowa Health Care System, Omaha, Nebraska, USA
[2]Department of Internal Medicine, Division of Rheumatology, University of Nebraska Medical Center, Omaha, Nebraska, USA
[3]Department of Biostatistics, University of Nebraska Medical Center, Omaha, Nebraska, USA
[4]Department of Medicine, Division of Rheumatology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA
[5]Rheumatology, Corporal Michael J Crescenz VA Medical Center, Philadelphia, Pennsylvania, USA
[6]Rheumatology, VA Salt Lake City Health Care System, Salt Lake City, Utah, USA
[7]Department of Medicine, Division of Rheumatology, University of Utah Medical Center, Salt Lake City, Utah, USA
[8]Rheumatology, VA Boston Healthcare System, West Roxbury, Massachusetts, USA
[9]Department of Internal Medicine, Division of Cardiology, University of Nebraska Medical Center, Omaha, Nebraska, USA

Acknowledgements Work supported by Centre of Excellence for Suicide Prevention, Joint Department of Veterans Affairs and Department of DefenseDefence Mortality Data Repository—National Death Index

Contributors TMJ, TRM and BRE designed the study. TMJ, JFB, PR, BS, TRM and BRE were responsible for acquisition of data. TMJ, HRS, PR, CZ and BRE analysed the data. All authors were responsible for interpretation of the data and for drafting, revising and approving the final submitted manuscript.

Funding TMJ was supported by a Rheumatology Research Foundation Resident Research Preceptorship. TRM is supported by a VA Merit Award (BX004600) and grants from the Rheumatology Research Foundation and the National Institutes of Health: National Institute of General Medical Sciences (U54GM115458), National Institute on Alcohol Abuse and Alcoholism (R25AA020818) and National Institute of Arthritis and Musculoskeletal and Skin Diseases (2P50AR60772). BRE is supported by a Rheumatology Research Foundation Scientist Development Award and the VA (CX002203).

Disclaimer The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

Competing interests MDG receives grant support from Bristol Myers Squibb for unrelated work.

Patient consent for publication Not required.

Ethics approval Each individual site has institutional review board approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request from the VA Rheumatoid Arthritis Registry and Biorepository after obtaining the required ethical approval.

ORCID iDs
Tate M Johnson http://orcid.org/0000-0003-0335-4157
Ted R Mikuls http://orcid.org/0000-0002-0897-2272
Bryant R England http://orcid.org/0000-0002-9649-3588

REFERENCES

1 England BR, Sayles H, Michaud K, *et al*. Cause-Specific mortality in male US veterans with rheumatoid arthritis. *Arthritis Care Res* 2016;68:36–45.
2 Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol* 2008;26:S35–61.
3 Aviña-Zubieta JA, Choi HK, Sadatsafavi M, *et al*. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum* 2008;59:1690–7.
4 Avina-Zubieta JA, Thomas J, Sadatsafavi M, *et al*. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis* 2012;71:1524–9.
5 Løgstrup BB, Ellingsen T, Pedersen AB, *et al*. Cardiovascular risk and mortality in rheumatoid arthritis compared with diabetes mellitus and the general population. *Rheumatology* 2021;60:1400–9.
6 Solomon DH, Karlson EW, Rimm EB, *et al*. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003;107:1303–7.
7 Ridker PM, Everett BM, Pradhan A, *et al*. Low-Dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019;380:752–62.
8 Roubille C, Richer V, Starnino T, *et al*. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:480–9.
9 Ajeganova S, de Faire U, Jogestrand T, *et al*. Carotid atherosclerosis, disease measures, oxidized low-density lipoproteins, and atheroprotective natural antibodies for cardiovascular disease in early rheumatoid arthritis -- an inception cohort study. *J Rheumatol* 2012;39:1146–54.
10 Davis LA, Cannon GW, Pointer LF, *et al*. Cardiovascular events are not associated with MTHFR polymorphisms, but are associated with methotrexate use and traditional risk factors in US veterans with rheumatoid arthritis. *J Rheumatol* 2013;40:809–17.
11 Widdifield J, Abrahamowicz M, Paterson JM, *et al*. Associations between methotrexate use and the risk of cardiovascular events in patients with Elderly-onset rheumatoid arthritis. *J Rheumatol* 2019;46:467–74.
12 Bernatsky S, Hudson M, Suissa S. Anti-Rheumatic drug use and risk of hospitalization for congestive heart failure in rheumatoid arthritis. *Rheumatology* 2005;44:677–80.
13 Myasoedova E, Crowson CS, Nicola PJ, *et al*. The influence of rheumatoid arthritis disease characteristics on heart failure. *J Rheumatol* 2011;38:1601–6.
14 Reiss AB, Carsons SE, Anwar K, *et al*. Atheroprotective effects of methotrexate on reverse cholesterol transport proteins and foam cell transformation in human THP-1 monocyte/macrophages. *Arthritis Rheum* 2008;58:3675–83.
15 Ronda N, Greco D, Adorni MP, *et al*. Newly identified antiatherosclerotic activity of methotrexate and adalimumab: complementary effects on lipoprotein function and macrophage cholesterol metabolism. *Arthritis Rheumatol* 2015;67:1155–64.
16 Thornton CC, Al-Rashed F, Calay D, *et al*. Methotrexate-mediated activation of an AMPK-CREB-dependent pathway: a novel mechanism for vascular protection in chronic systemic inflammation. *Ann Rheum Dis* 2016;75:439–48.
17 Zimmerman MC, Clemens DL, Duryee MJ, *et al*. Direct antioxidant properties of methotrexate: inhibition of malondialdehyde-acetaldehyde-protein adduct formation and superoxide scavenging. *Redox Biol* 2017;13:588–93.
18 Mikuls TR, Reimold A, Kerr GS, *et al*. Insights and implications of the Va rheumatoid arthritis registry. *Fed Pract* 2015;32:24–9.
19 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.
20 , 2014. Available: http://www.hsrd.research.va.gov/for_researchers/vinci/cdw.cfm [Accessed cited 2018 November 21].
21 Cannon GW, Mikuls TR, Hayden CL, *et al*. Merging Veterans Affairs rheumatoid arthritis registry and pharmacy data to assess methotrexate adherence and disease activity in clinical practice. *Arthritis Care Res* 2011;63:1680–90.
22 England BR, Sayles H, Mikuls TR, *et al*. Validation of the rheumatic disease comorbidity index. *Arthritis Care Res* 2015;67:865–72.
23 Baker JF, Billig E, Michaud K, *et al*. Weight loss, the obesity paradox, and the risk of death in rheumatoid arthritis. *Arthritis Rheumatol* 2015;67:1711–7.
24 Davis LA, Mann A, Cannon GW, *et al*. Validation of diagnostic and procedural codes for identification of acute cardiovascular events in US veterans with rheumatoid arthritis. *EGEMS* 2013;1:8.
25 Floyd JS, Blondon M, Moore KP, *et al*. Validation of methods for assessing cardiovascular disease using electronic health data in a cohort of veterans with diabetes. *Pharmacoepidemiol Drug Saf* 2016;25:467–71.

26 Grijalva CG, Chung CP, Stein CM, *et al*. Computerized definitions showed high positive predictive values for identifying hospitalizations for congestive heart failure and selected infections in Medicaid enrollees with rheumatoid arthritis. *Pharmacoepidemiol Drug Saf* 2008;17:890–5.
27 Huang H, Turner M, Raju S, *et al*. Identification of acute decompensated heart failure hospitalizations using administrative data. *Am J Cardiol* 2017;119:1791–6.
28 Kiyota Y, Schneeweiss S, Glynn RJ, *et al*. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. *Am Heart J* 2004;148:99–104.
29 Lakshminarayan K, Larson JC, Virnig B, *et al*. Comparison of Medicare claims versus physician adjudication for identifying stroke outcomes in the women's health Initiative. *Stroke* 2014;45:815–21.
30 Sundbøll J, Adelborg K, Munch T, *et al*. Positive predictive value of cardiovascular diagnoses in the Danish national patient registry: a validation study. *BMJ Open* 2016;6:e012832.
31 Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11:550–60.
32 Fewell Z, Hernán MA, Wolfe F, *et al*. Controlling for time-dependent confounding using marginal structural models. *Stata J* 2004;4:402–20.
33 Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. *Stat Med* 2007;26:734–53.
34 Ridker PM, Everett BM, Thuren T, *et al*. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377:1119–31.
35 Pearl J. Interpretation and identification of causal mediation. *Psychol Methods* 2014;19:459–81.
36 Micha R, Imamura F, Wyler von Ballmoos M, *et al*. Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. *Am J Cardiol* 2011;108:1362–70.
37 Ahlers MJ, Lowery BD, Farber-Eger E, *et al*. Heart failure risk associated with rheumatoid Arthritis-Related chronic inflammation. *J Am Heart Assoc* 2020;9:e014661.
38 Crowson CS, Nicola PJ, Kremers HM, *et al*. How much of the increased incidence of heart failure in rheumatoid arthritis is attributable to traditional cardiovascular risk factors and ischemic heart disease? *Arthritis Rheum* 2005;52:3039–44.
39 Davis JM, Roger VL, Crowson CS, *et al*. The presentation and outcome of heart failure in patients with rheumatoid arthritis differs from that in the general population. *Arthritis Rheum* 2008;58:2603–11.
40 Khalid U, Egeberg A, Ahlehoff O, *et al*. Incident heart failure in patients with rheumatoid arthritis: a nationwide cohort study. *J Am Heart Assoc* 2018;7. doi:10.1161/JAHA.117.007227. [Epub ahead of print: 19 01 2018].
41 Mantel Ängla, Holmqvist M, Andersson DC, *et al*. Association Between Rheumatoid Arthritis and Risk of Ischemic and Nonischemic Heart Failure. *J Am Coll Cardiol* 2017;69:1275–85.
42 Nicola PJ, Maradit-Kremers H, Roger VL, *et al*. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. *Arthritis Rheum* 2005;52:412–20.
43 Heidenreich PA, Albert NM, Allen LA, *et al*. Forecasting the impact of heart failure in the United States: a policy statement from the American heart association. *Circ Heart Fail* 2013;6:606–19.
44 England BR, Thiele GM, Anderson DR, *et al*. Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications. *BMJ* 2018;361:k1036.
45 Xie F, Chen L, Yun H, *et al*. Benefits of methotrexate use on cardiovascular disease risk among rheumatoid arthritis patients initiating biologic disease-modifying antirheumatic drugs. *J Rheumatol* 2020. doi:10.3899/jrheum.191326. [Epub ahead of print: 15 Oct 2020].
46 Tardif J-C, Kouz S, Waters DD, *et al*. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019;381:2497–505.
47 Li Y, Huang T, Zheng Y, *et al*. Folic acid supplementation and the risk of cardiovascular diseases: a Meta-Analysis of randomized controlled trials. *J Am Heart Assoc* 2016;5.
48 Baker JF, England BR, George M, *et al*. Disease activity, cytokines, chemokines and the risk of incident diabetes in rheumatoid arthritis. *Ann Rheum Dis* 2021;80:566–72.
49 Johnson SR, Tomlinson GA, Hawker GA, *et al*. Propensity score methods for bias reduction in observational studies of treatment effect. *Rheum Dis Clin North Am* 2018;44:203–13.

CLINICAL SCIENCE

Abatacept is second to rituximab at risk of HBsAg reverse seroconversion in patients with rheumatic disease

Ming-Han Chen ,[1,2] I-Cheng Lee,[2,3] Ming-Huang Chen,[2] Ming-Chih Hou,[3] Chang-Youh Tsai ,[1,2] Yi-Hsiang Huang [3,4]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220774).

[1]Division of Allergy, Immunology, & Rheumatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[2]Faculty of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
[3]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[4]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

Correspondence to
Professor Yi-Hsiang Huang, Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; yhhuang@vghtpe.gov.tw and Dr Ming-Han Chen, Division of Allergy, Immunology, & Rheumatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; meikankimo@yahoo.com.tw

Received 13 May 2021
Accepted 18 June 2021
Published Online First 29 June 2021

To cite: Chen M-H, Lee I-C, Chen M-H, *et al*. *Ann Rheum Dis* 2021;**80**:1393–1399.

ABSTRACT

Background Hepatitis B surface antigen (HBsAg) reverse seroconversion (RS) can happen in patients with rheumatoid arthritis (RA) with resolved hepatitis B (RHB) undergoing biological disease-modifying antirheumatic drugs (bDMARDs). But the incidence and risk factors need to be delineated.

Methods From 2003 to 2019, 1937 patients with RA with available HBsAg and antibody to hepatitis B virus (HBV) core antigen data were retrospectively reviewed, and 489 patients with RHB undergoing bDMARDs treatment were identified. Factors associated with HBsAg RS were analysed.

Results During 67 828 person-months of follow-up, 27 (5.5%) patients developed HBsAg RS after bDMARD treatment. As compared with those without HBsAg RS, patients with HBsAg RS were older, had lower frequency of antibody to HBsAg (anti-HBs), and lower baseline anti-HBs levels. In multivariate analysis, rituximab, abatacept and baseline negative for anti-HBs were the independent risk factors for HBsAg RS (adjusted HR: 87.76, 95% CI: 11.50 to 669.73, p<0.001; adjusted HR: 60.57, 95% CI: 6.99 to 525.15, p<0.001; adjusted HR: 5.15, 95% CI: 2.21 to 12.02, p<0.001, respectively). The risk of HBsAg RS was inversely related to the level of anti-HBs. Both rituximab and abatacept might result in anti-HBs loss, and abatacept had a cumulative incidence of HBsAg RS of 35.4%–62.5% in patients with low titers or negative of anti-HBs.

Conclusions Not only rituximab, but also abatacept has a high risk of HBV reactivation in patient with RA with RHB. Anti-HBs positivity cannot confer HBV reactivation-free status if the anti-HBs levels are not high enough for patients with RHB on rituximab and abatacept treatment.

Key messages

What is already known about this subject?
- Hepatitis B surface antigen (HBsAg) reverse seroconversion (RS) can happen in patients with resolved hepatitis B (RHB) receiving immunosuppressive treatment.
- Rituximab is at the highest risk to induce HBsAg RS among biological agents.

What does this study add?
- Antibody to hepatitis B surface antigen (anti-HBs) positivity cannot confer hepatitis B virus (HBV) reactivation-free status.
- Not only rituximab, but also abatacept has high risk of HBsAg RS, through loss of anti-HBs.

How might this impact on clinical practice or future developments?
- Abatacept should be classified as high risk of HBV reactivation in RHB cases if anti-HBs levels are not high enough, at which, antiviral prophylaxis is highly recommended.
- Anti-HBs monitoring should be included for patients with RHB on rituximab and abatacept treatment.

INTRODUCTION

Hepatitis B virus (HBV) infection is a global health problem which can cause acute or chronic hepatitis, liver cirrhosis and hepatocellular carcinoma, and contributes to over 1 million deaths per year worldwide.[1 2] It is estimated that 257 million people worldwide are chronic infected by HBV, while far more than this numbers have prior HBV exposure.[1] For patients with resolved hepatitis B (RHB) infection, defined as hepatitis B surface antigen (HBsAg)-negative, and antibody to hepatitis B core antigen (anti-HBc)-positive, HBsAg reverse seroconversion (RS) may occur in those receiving chemotherapy or immunosuppressive treatment.[3–5] The incidence of HBsAg RS in patients with RHB with haematological malignancy is heterogeneous, with 3%–50% in patients receiving chemotherapy alone or combined with B-cell depleting therapy.[4–7]

Rheumatoid arthritis (RA) is the most common type of chronic inflammatory arthritis and affects about 1% of the worldwide population.[8] To reduce synovial inflammation and attenuate bone destruction, most of them receive lifelong immunosuppressive therapy, including glucocorticoid (GC) and synthetic disease-modifying antirheumatic drugs (sDMARDs), and biological DMARDs (bDMARDs). bDMARDs are more effective at treating RA but carry an increased risk of infections.[9] The risk of HBV reactivation (HBVr) in patients with RA with chronic hepatitis B (CHB) increases by bDMARDs and is the highest among those receiving B-cell-depleting therapies, and GC treatment in combination with bDMARDs.[10–14] In contrast, only a few cases of HBsAg RS in patients with RHB with RA after anti-tumour necrosis factor (TNF)-α, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)-immunoglobulin (Ig) fusion

protein (abatacept), or B-cell-depleting (anti-CD20 monoclonal antibody, rituximab) treatment were reported to date.[11 15 16] The American Gastroenterological Association (AGA) Institute proposed that patients with CHB or RHB on B-cell-depleting therapies considered to be at a high risk of HBVr, while those on TNF-α inhibitors or CTLA-4-Ig are classified as moderate risk of HBVr.[17 18] However, the evidences regarding the risk were mainly based on patients with malignancy and few case series studies of patients with rheumatic diseases with small sample size and short follow-up. Informative data regarding the risk of HBsAg RS among patients with RA with RHB remain limited.

We recently described clinical features and outcomes of HBsAg RS for patients with RHB RA who received immunosuppressant or bDMARD therapy.[16] However, the incidence of HBsAg RS by different classes of bDMARDs and factors associated with HBsAg RS remain unknown. Through an extended long-term follow-up data, this study aimed to determine the occurrence rate of HBsAg RS and identify risk factors for HBsAg RS among patients with RA with RHB who received bDMARD therapy.

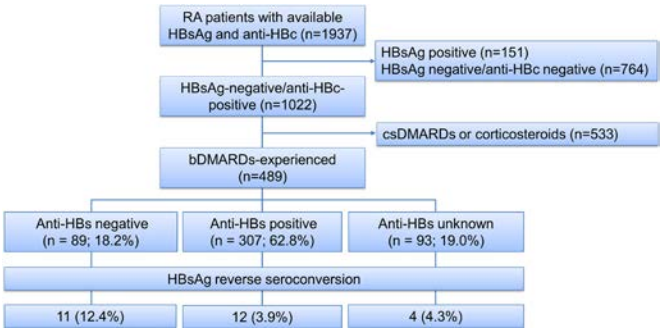


Figure 1 Study flowchart. All patients with RA were screened for their HBsAg and antibody to hepatitis B core antigen before immunosuppressive treatment. Resolved hepatitis B virus infected patients who were treated with bDMARDs were enrolled and categorised according to the status of anti-HBs. HBsAg reverse seroconversion was defined as reappearance of HBsAg. anti-HBs, antibody to HBsAg; bDMARDs, biological disease-modifying anti-rheumatic drugs; csDMARDs, conventional synthetic DMARDs; HBsAg, hepatitis B surface antigen; RA, rheumatoid arthritis.

PATIENTS AND METHODS

Patients

We retrospectively investigated 1937 patients with RA who had available HBsAg and anti-HBc data in Taipei Veterans General Hospital between June 2003 and May 2019, 1022 patients were classified as RHB with HBsAg-negative/anti-HBc-positive at the time of diagnosis or before immunosuppressive treatment for RA.[19] Among them, 487 patients ever received bDMARDs treatment. None received anti-HBV prophylaxis by nuceos(t)ide analogues (NUCs) as it has not been reimbursed for RHB by Taiwan National Health Insurance (TNHI) up to now. Liver function was regularly monitored every 2–3 months, and HBsAg status was determined biannually after starting immunosuppressive treatment. The detailed medical records, including immunological profiles, clinical courses and outcomes, were carefully reviewed. All patients met the 1987 ACR criteria[20] or 2010 ACR/EULAR classification criteria for RA.[21]

Immunosuppressive therapy for RA

sDMARDs included methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, while the bDMARDs included anti-TNF-α agents, abatacept, rituximab and anti-interleukin-6 (IL-6) receptor monoclonal antibody (tocilizumab). bDMARDs were administered at standard dosages as our previous report.[16] bDMARDs were indicated in diseases refractory to conventional therapy, which was defined as sDMARD therapy for over 6 months. A drug exposure was defined as a patient receiving GC, sDMARDs, or bDMARDs for more than 4 weeks.

Definition

HBsAg RS was defined as reappearance of HBsAg in the serum in patients with RHB. Hepatitis flare was defined as a serum alanine aminotransferase (ALT) level at least twice the baseline level and more than threefold upper limit normal (ULN). The ULN for ALT was 40 U/L. Patients with RA may switch to a different bDMARD over time, the one used at the end of follow-up, or at the time when HBsAg RS occurred, was counted as the candidate biologics. The medical recorded of the date at the beginning of immunosuppressive treatment was defined as baseline data.

Serological tests of viral hepatitis markers (online supplemental materials)

Statistical analysis

The duration of the patient's follow-up was calculated from the time of immunosuppressive treatment for RA to the date of HBsAg RS, the last visit or death. The occurrence of HBsAg RS was carefully reviewed since starting bDMARD treatments for all the studied cases. Fisher's exact tests were used to compare categorical variables. An independent Student's t-test was used to compare numerical data following a normal distribution and Mann-Whitney U test was used for data violating the normal distribution. The cumulative incidence of HBsAg RS was estimated using the Kaplan-Meier method and the statistical differences were tested by log-rank tests. Analysis of factors for HBsAg RS was performed using the Cox proportional hazards model. Covariates with a significance of <0.2 in the univariate logistic regression analyses were further introduced into a multivariable model with automatic backward elimination. A p value <0.05 was considered as statistically significant. All statistical analyses were conducted using SPSS software V.26.0 (IBM SPSS Statistics for Windows, IBM, Armonk, New York, USA).

Patient and public involvement

Patients were not involved in the study.

RESULTS

Study population

There were 1022 patients identified to be RHB (figure 1). Of them, 489 patients had undergone bDMARDs treatment, including 403 (82.4%) females, with the mean age of 51.8 years at diagnosis of RA (table 1). Of the 396 patients with available anti-HBs data, 307 (77.5%) were positive for anti-HBs before receiving immunosuppressive treatment. Of them, 188 (38.4%) patients received GC therapy, while 445 (91.0%) patients had sDMARDs during bDMARD treatment; 153 (31.3%) patients had experienced more than one bDMARD. bDMARD use at the end of follow-up or at the time when HBsAg RS developed were counted, including 255 TNF-α inhibitors, 69 abatacept, 81 tocilizumab and 84 rituximab. The median time from starting immunosuppressant and bDMARD treatment to the end of the follow-up was 153 (range: 18–196) and 77 (range: 3–196) months, respectively.

Table 1 Demographic and immunologic profiles of 487 patients with RHB with RA with or without HBsAg RS

Characteristic	Total N=489	HBsAg RS+ n=27	HBsAg RS− n=462	P value
Baseline characteristics				
Age at diagnosis of RA (years), mean±SD	51.8±12.4	57.7±11.5	51.5±12.4	0.012*
Female, n (%)	403 (82.4)	22 (81.5)	381 (82.5)	0.800
Baseline anti-HBs positive, n (%)	307/396 (77.5)	12/23 (52.2)	295/373 (79.1)	0.007*
Baseline anti-HBs (mIU/mL), median (range)	45.8 (0.1–>1000)	10.8 (0.1–118.5)	54.3 (0.2–>1000)	<0.001*
Baseline ALT (U/L), mean±SD	20.3±8.1	21.9±7.7	20.3±8.1	0.204
Baseline AST (U/L), mean±SD	22.9±6.7	24.4±6.5	22.8±6.8	0.174
Baseline total bilirubin (mg/dL), mean±SD	0.41±0.17	0.41±0.16	0.40±0.17	0.790
Rheumatoid factor positive, n (%)	409 (83.6)	23 (85.2)	386 (83.5)	1.000
Anticyclic citrullinated peptide antibody positive, n (%)	234/301 (77.7)	14/17 (82.4)	220/284 (77.5)	0.772
Disease activity				
ESR (mm/hour), mean±SD	55.0±23.4	50.4±28.0	55.3±23.1	0.415
CRP (mg/dL), median (range)	1.8 (0.0–15.9)	1.4 (0.0–7.2)	1.8 (0.0–15.9)	0.132
Immunosuppressants during bDMARD treatment, n (%)				
Glucocorticoid	188 (38.4)	15 (55.6)	173 (37.4)	0.068
sDMARDs	445 (91.0)	25 (92.6)	420 (90.9)	1.000
Methotrexate	252 (51.5)	18 (66.7)	234 (50.6)	0.117
Leflunomide	83 (17)	1 (3.7)	82 (17.7)	0.065
Hydroxychloroquine	251 (51.3)	16 (59.3)	235 (50.9)	0.434
Sulfasalazine	154 (32.1)	11 (40.7)	143 (31.6)	0.396
More than one bDMARD treatment, n (%)	153 (31.3)	19 (70.4)	134 (29.0)	<0.001*
bDMARDs at the end of follow-up, n (%)				
TNF-α inhibitors	255 (52.1)	3 (11.1)	252 (54.5)	
Etanercept	105 (21.5)	1 (3.7)	104 (22.5)	
Adalimumab	115 (23.5)	2 (7.4)	113 (24.5)	
Golimumab	35 (7.2)	0 (0.0)	35 (7.6)	
Abatacept	69 (14.1)	6 (22.2)	63 (13.6)	
Tocilizumab	81 (16.6)	0 (0.0)	81 (17.5)	
Rituximab	84 (17.2)	18 (66.7)	66 (14.3)	
Duration of follow-up (months), median (range)	153 (18–196)	131 (20–196)	154 (18–196)	0.232
Duration of biologic therapy (months), median (range)	77 (3–196)	90 (10–174)	76 (3–196)	0.577

*P<0.05.
ALT, alanine aminotransferase; anti-HBs, antibody to HBsAg; AST, aspartate aminotransferase; bDMARDs, biological disease-modifying antirheumatic drugs; CRP, c-reactive protein; ESR, erythrocytes sedimentation rate; RA, rheumatoid arthritis; HBsAg RS, hepatitis B surface antigen reverse seroconversion; sDMARDs, synthetic disease-modifying antirheumatic drugs; TNF-α, tumour necrosis factor-α.

Baseline characteristics of patients with RA with or without HBsAg RS

During 67 828 person-months of follow-up, 27 (5.5%) out of 489 patients developed HBsAg RS, with the incidence of 0.04 per 100 person-months. Among them, 18 patients were related to rituximab, 6 by abatacept, 2 by adalimumab and 1 by etanercept. The median intervals from the start of immunosuppressants or bDMARDs to HBsAg RS were 131 (range: 20–196) and 90 (range: 10–174) months, respectively (table 1). The cumulative risks of HBsAg RS were 2.4% at 10 years, and 11.3% at 16 years (figure 2A).

Patients with HBsAg RS were older and had significantly lower baseline anti-HBs levels than those without HBsAg RS (p=0.012 and <0.001, respectively). The frequency of anti-HBs positivity was significantly lower in patients with HBsAg RS as compared with those without HBsAg RS (52.2% vs 79.1%, p=0.007, table 1).

Of the 27 cases with HBsAg RS, 19 (70.4%) had received more than one bDMARDs and the median time from switching bDMARD to HBsAg RS was 67 months (range: 9 to 99 months). Patients with HBsAg RS were more frequently to receive more than one bDMARD (p<0.001). However, the frequency of GC and sDMARD use was similar between patients with and without HBsAg RS (table 1).

Incidence of HBsAg RS by different bDMARDs

The incidence of HBsAg RS was the highest by rituximab, followed by abatacept, TNF-α inhibitors and tocilizumab (incidence: 17.717, 9.375, 0.992 and 0.000 per 1000 patient-years, respectively) (table 2) with the 16-year cumulative risks of HBsAg RS of 51.0%, 19.7%, 2.4%, 0.0%, respectively (figure 2B). The risk of HBsAg RS was significantly higher by rituximab (adjusted HR: 35.646, 95% CI: 8.158 to 155.758, p<0.001) and abatacept (adjusted HR: 15.394, 95% CI 3.076 to 77.037, p=0.001) as compared with TNF-α inhibitors (table 2).

Factors associated with HBsAg RS in patients with RA with RHB

In univariate analysis, baseline negative for anti-HBs, and GC use during bDMARD treatment were associated with the risk of HBsAg RS with the unadjusted HR of 3.117 (p=0.007) and 2.226 (p=0.044), respectively (table 3). Of various bDMARDs, rituximab and abatacept had higher risk of HBsAg RS, comparing

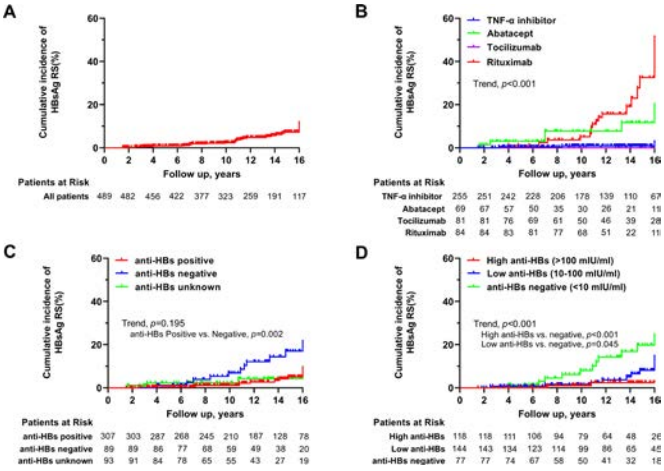


Figure 2 Cumulative risk of HBsAg RS in patients with RA with resolved HBV infection. (A) Cumulative risk of HBsAg RS in 489 patients with RA with resolved HBV infection who were treated with bDMARDs. (B) Cumulative risk of HBsAg RS stratified by classes of bDMARDs. (C) Cumulative risk of HBsAg RS stratified by the status of baseline anti-HBs. (D) Cumulative risk of HBsAg RS stratified by baseline levels of anti-HBs. Patients were categorised into high (>100 mIU/mL), low (10–100 mIU/mL) and negative anti-HBs (<10 mIU/mL) groups for analysis the cumulative risk of HBsAg RS was evaluated by Kaplan-Meier analysis and log-rank test. anti-HBs, antibody to HBsAg; bDMARDs, biological disease-modifying anti-rheumatic drugs; HBsAg RS, hepatitis B surface antigen reverse seroconversion; TNF-α, tumour necrosis factor-α.

to other bDMARDs (HR: 10.645, p<0.001 and HR: 2.775, p=0.029, respectively). In multivariate analysis, rituximab, abatacept and baseline negative for anti-HBs were the independent risk factors for HBsAg RS after adjusting other covariates (adjusted HR: 87.757, 95% CI: 11.499 to 669.733, p<0.001; adjusted HR: 60.572, 95% CI: 6.987 to 525.150, p<0.001; and adjusted HR: 5.151, 95% CI: 2.207 to 12.023, p<0.001, respectively) (figure 2A and C). Patients experienced with more than one bDMARD had a higher risk to develop HBsAg RS when compared with those with single bDMARD therapy in univariate analysis (HR: 4.574, p<0.001). However, it became non-significant after adjusting for other confounders.

To determine the role of baseline anti-HBs level in the risk of HBsAg RS, patients were categorised into high (>100 mIU/mL), low (10–100 mIU/mL) and anti-HBs negative (<10 mIU/mL) groups for comparison.[22] As shown in figure 2D, the cumulative risk of HBsAg RS at year 16 were 24.3%, 14.2% and 2.4% for patients with RA with baseline anti-HBs-negative, anti-HBs low, and anti-HBs high, respectively (p<0.001).

The level of anti-HBs associated with the risk of HBsAg RS in subgroups

For rituximab-treated patients, the incidence of HBsAg RS was up to 53.3% for patients negative for baseline anti-HBs, 20.6% for patients with low anti-HBs, while only 8.3% in patients with high anti-HBs (p<0.001, figure 3A), with the 16-year cumulative risk of HBsAg RS up to 100.0% and 43.1% in patients with anti-HBs-negative and low anti-HBs level (p=0.005, figure 3B). While the 16-year cumulative risk of HBsAg RS was still high (10.5%) in patients with baseline high anti-HBs level. In abatacept-treated patients, no patient with high baseline anti-HBs, while 3 (14.3%) out of 21 patients with low anti-HBs, and 2 (28.6%) of 7 patients negative for baseline anti-HBs experienced HBsAg RS (figure 3C), with the cumulative risk of HBsAg RS at year 16 of 0%, 35.4% and 62.5% for patients with RA with baseline anti-HBs high, low and negative groups (p=0.026, figure 3D). In other bDMARD-treated patients, the risk of HBsAg RS was generally low, regardless the baseline anti-HBs level. However, HBsAg RS was only detected in patients negative for baseline anti-HBs (figure 3E,F).

Incidence of anti-HBs loss by bDMARD treatment

Baseline anti-HBs status was associated with the risk of HBsAg RS, we further explored the incidence of anti-HBs loss during the bDMARD treatment. As shown in figure 4A, 20 (10.2%) out of 197 patients experienced anti-HBs loss during bDMARD treatment. Of note, the incidences of anti-HBs loss in patients receiving rituximab and abatacept were high (24.6% and 15.0%, respectively, figure 4A).

In general, a high baseline anti-HBs level (>100 mIU/mL) was associated with lower risk of anti-HBs loss (1.8% vs 20.5%, p<0.001, figure 4B). Similar trend was observed in abatacept-treated group (0% vs 33.3%, p=0.074, figure 4C) and in rituximab-treated patients (8.3% vs 36.4%, p=0.027, figure 4D).

Outcomes of the patients with RA with HBsAg RS

Of the 27 patients with RA with HBsAg RS, 15 (57.7%) of 26 individuals would become HBeAg-positive after HBV reactivation (online supplemental table 1). The median peak HBV viral loads was 19 300 000 IU/mL (ranged from 1370 to >170 000 000 IU/mL). Twelve (44.0%) experienced hepatitis flare, while 11 (40.7%) and 6 (22.2%) had a more than five-fold and tenfold ULN ALT elevation, respectively. Six (22.2%) patients had liver decompensation with hepatitis flare accompanied by a total bilirubin level >2 mg/dL and/or a prolongation of the patient's prothrombin time >3 s. The principal to manage patients with HBVr included discontinuation of bDMARDs at the time of HBsAg RS, and promptly referral to hepatologists.

Table 2 Crude incidence rates and HR of HBsAg RS among patients with RA with RHB receiving different biologics

Exposure*	Number of events	Person-years†	IR (per 1000 person-years)	Adjusted HR (95% CI)‡	P value
TNF-α inhibitors	3	3023	0.992	Reference	
Tocilizumab	0	947	0.000	–	–
Abatacept	6	640	9.375	15.394 (3.076 to 77.037)	0.001§
Rituximab.	18	1016	17.717	35.646 (8.158 to 155.758)	<0.001§

*The biological disease-modifying antirheumatic drugs at the end of follow-up or the time when HBsAg RS developed.
†The duration was defined as the period from initiation of immunosuppressive treatment to the final follow-up visit or the time of HBsAg RS.
‡HR was adjusted for age at RA diagnosis >50 years and sex.
§P<0.05.
.HBsAg RS, hepatitis B surface antigen reverse seroconversion; IR, incidence rate; RA, rheumatoid arthritis; RHB, resolved hepatitis B; TNF-α, tumour necrosis factor-α.

Table 3 Factors associated with HBsAg RS among 487 patients with RA with RHB in univariate analysis and multivariable model

Predictors	Total (n=489), n (%)	HBsAg RS (n=27), n (%)	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Age at RA diagnosis, ≥50 years	289 (59.1)	19 (70.4)	2.383 (1.037 to 5.478)	0.041		
Age at bDMARDs use, ≥50 years	395 (80.8)	25 (92.6)	3.014 (0.712 to 12.762)	0.134		
Gender, female	403 (82.4)	22 (81.5)	0.744 (0.275 to 2.014)	0.561		
Baseline anti-HBs						
Positive	307 (77.5)	12 (52.2)	1		1	<0.001*
Negative	89 (22.5)	11 (47.8)	3.117 (1.367 to 7.106)	0.007*	5.151 (2.207 to 12.023)	
Unknown	93	4	1.458 (0.463 to 4.592)	0.519		
Baseline ALT, ≥30 U/L	61 (12.5)	6 (22.5)	1.606 (0.637 to 4.048)	0.315		
Baseline AST, ≥30 U/L	78 (16.0)	5 (18.5)	0.999 (0.373 to 2.673)	0.998		
GC during bDMARD treatment	188 (38.4)	15 (55.6)	2.226 (1.021 to 4.852)	0.044		
sDMARDs during bDMARD treatment	445 (91.0)	25 (92.6)	3.054 (0.413 to 22.609)	0.274		
More than one bDMARD treatment	153 (31.3)	19 (70.4)	4.574 (1.999 to 10.470)	<0.001*	1.597 (0.371 to 6.867)	0.530
Abatacept use	69 (14.1)	6 (22.2)	2.775 (1.110 to 6.941)	0.029*	60.572 (6.987 to 525.150)	<0.001*
Rituximab use	84 (17.2)	18 (66.7)	10.645 (4.677 to 24.229)	<0.001*	87.757 (11.499 to 669.733)	<0.001*

Covariates with a significance of <0.2 in the univariate logistic regression analyses were introduced into a multivariable model with automatic backward elimination.
*P<0.05.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; bDMARDs, biological disease-modifying antirheumatic drugs; GC, glucocorticoid; RA, rheumatoid arthritis; RHB, resolved hepatitis B; sDMARD, synthetic disease-modifying antirheumatic drugs.

High-potency NUCs, entecavir or tenofovir, were provided immediately for up to 3 years if they fulfilled the TNHI criteria. In patients with sign of liver decompensation, liver transplantation evaluation would start soon when feasible. Even though, one (3.7%) patient expired in this cohort. The patient was a 63-year-old man with hypertension history undergoing adalimumab for 8 months and died from HBVr even under entecavir rescue treatment. No specific factor was identified to be associated with severe ALT flare (online supplemental table 2).

DISCUSSION

Although bDMARD therapy would increases the risk of HBsAg RS in patients with RA with RHB, the incidence and risk factors associated with HBsAg RS have not been well investigated before due to lack of long-term observation. A prospective study including 179 Italian patients with rheumatic diseases with RHB did not detect any HBsAg RS case during a median follow-up of 2.7 years in patients on rituximab, and 4.6 years in patients on TNF-α inhibitors.[23] Our data showed that long-term bDMARDs treatment would indeed result in HBsAg RS among patients with RA with RHB, with an incidence rate of 5.5% in the bDMARD-treated cohort. The median time from immunosuppressants treatment initiation to HBsAg RS was up to 11 years, while median time from bDMARD use to HBsAg RS was almost 8 years. The finding that HBsAg RS in patients with RHB with RA occurred after long-term bDMARD therapy may explain why previous studies did not detect the event. To the best of our knowledge, the current study is the largest cohort study with the longest follow-up period to investigate the incidence of HBsAg RS in patients with RA with RHB.

This study is also the first attempt to compare the incidence of HBsAg RS among different biologics by mass screening. Among patients with RHB with bDMARD treatment, not only rituximab, but also abatacept has a high risk of HBsAg RS. Rituximab is well known for its association with a high risk of HBVr in patients with lymphoma with RHB.[5 17] Rituximab is classified as high-risk agent for HBVr by the AGA and American Association for the Study of Liver Diseases institutes.[17 18 24] Most of the reports also suggested that rituximab can induce HBVr in patients with RA, but few considered not.[25 26] The incidences of HBVr were 6.0% (3 of 50) to 9.1% (4 of 44) during the mean follow-up of 3.1–3.4 years in previous studies.[27 28] Our data showed that up to 21.4% (18 out of 84) patients with RA undergo rituximab treatment would develop HBsAg RS. High incidence of HBsAg RS in our study might result from a longer follow-up period. It is worth to note that the median time from rituximab use to HBsAg RS was 5.5 years (ranged: 9–99 months), supporting that long-term monitoring for HBV status is needed once biologics are initiated.

Abatacept, a blocker of T-cell activation, can induce HBVr in patients with RHB.[16] In three previous studies including 65 patients with RA with RHB without NUCs prophylaxis, only one experienced HBsAg RS during abatacept treatment.[23 29 30] In our cohort, abatacept is second to rituximab with a high risk of HBsAg RS in patients with RA with RHB. The cumulative incidence of HBsAg RS was around 20% in patients on abatacept treatment without high titers of anti-HBs. Previous studies revealed that HBV clearance depends on effective and vigorous HBV-specific $CD4^+$ and $CD8^+$ T cells.[31 32] CTLA-4 can interfere HBV-specific T-cell response.[33] Taking together, abatacept might abrogate the function of pre-existed CD4 and CD8 T cells and results in a high risk of HBsAg RS.

The risk of HBVr by TNF-α inhibitors in patients with CHB with rheumatic diseases has been well-demonstrated before, while the incidence is extremely low in patients with RHB. In our study, only 3 (1.2%) of the 255 patients with RA on anti-TNF-α treatment developed HBsAg RS during 1879 patient-years of follow-up.

In the present study, not only anti-HBs positivity, but also a high baseline anti-HBs level (>100 mIU/mL) was required to protect patients with RA with RHB from HBsAg RS. The risk of HBsAg RS was inversely related to the level of anti-HBs when receiving bDMARDs, including rituximab and abatacept. It is worth noting that the risk of HBsAg RS was still high (10.5%) in patients who were anti-HBs-high, HBsAg-negative/anti-HBc-positive and on rituximab treatment due to a high incidence of anti-HBs loss. For abatacept-treated patients with RA, the cumulative risk of HBsAg RS was also high if the baseline anti-HBs was low (≤100 mIU/mL), and anti-HBs loss would happen in cases with low baseline anti-HBs level. Consequently,

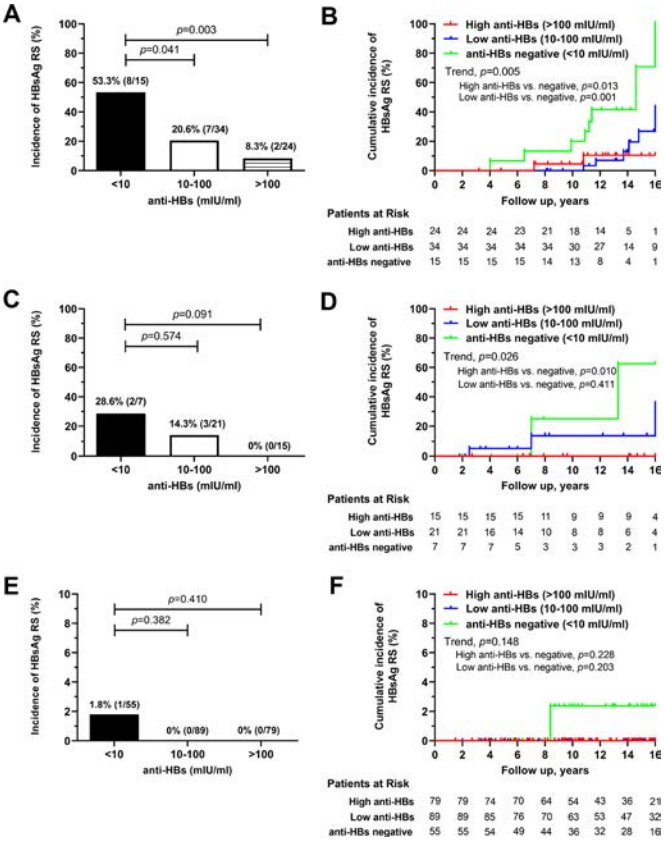


Figure 3 Incidence and cumulative risk of HBsAg RS in patients with RA with resolved hepatitis B virus infection stratified by baseline levels of anti-HBs. Incidence (A) and cumulative risk (B) of HBsAg RS stratified by baseline levels of anti-HBs for patients on rituximab treatment. Incidence (C) and cumulative risk (D) of HBsAg RS stratified by baseline levels of anti-HBs for patients on abatacept treatment. Incidence (E) and cumulative risk (F) of HBsAg RS stratified by baseline levels of anti-HBs for patients on other biological disease-modifying anti-rheumatic drugs. The cumulative risk of HBsAg RS was evaluated by Kaplan-Meier analysis and log-rank test. anti-HBs, antibody to HBsAg; HBsAg RS, hepatitis B surface antigen reverse seroconversion; RA, rheumatoid arthritis.

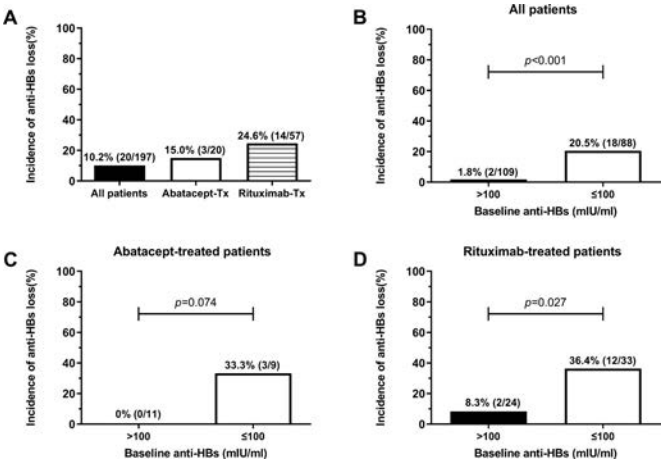


Figure 4 Proportion of anti-HBs loss in patients with rheumatoid arthritis. (A) Proportion of anti-HBs loss in all patients, on abatacept, and on rituximab treatment. (B) Proportion of the anti-HBs loss stratified by baseline levels of anti-HBs (>100 versus ≤100 mIU/mL) in all patients (C) on abatacept and (D) on rituximab treatment. anti-HBs, antibody to HBsAg.

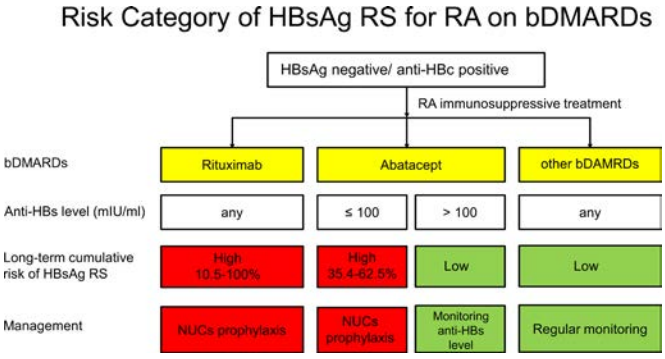


Figure 5 Risk category and management recommendation of HBsAg RS for patients with RA on bDMARDs based on long-term cumulative risk. HBsAg RS was defined as reappearance of HBsAg. bDMARDs, biological disease modifying anti-rheumatic drugs; HBsAg RS, hepatitis B surface antigen reverse seroconversion; NUCs, nuceos(t)ide analogue; RA, rheumatoid arthritis.

prophylactic NUCs is highly recommended for these patients. In general, the risk of HBsAg RS was low on other bDMARDs (eg, TNF-α inhibitors) regardless the anti-HBs level. Therefore, we propose an algorithm to stratify the risk of HBsAg RS and recommend how to manage patients with RHB on bDMARD treatment (figure 5).

Anti-HBs titers have been found to decline and loss in patients with haematological malignancies after receiving B-cell depleting treatment.[34] Among patients with baseline anti-HBs in high level, up to 8.3% patients on rituximab treatment lost anti-HBs, while none of the patients with baseline anti-HBs in high level on abatacept treatment experienced anti-HBs loss. It is worth noting that over 30% of patients on rituximab or abatacept treatment lost anti-HBs if their baseline anti-HBs was less than 100 mIU/mL. We recently demonstrated that abatacept binding to CD80/CD86 may negatively regulate antigen-specific B-cell function directly.[35] Indeed, anticitrullinated protein antibody levels significantly decreased after treatment with abatacept.[36] These may partially explain why abatacept decreased anti-HBs levels and then induced HBsAg RS.

There are some limitations. First, this is a retrospective study and the incidence of HBsAg RS might be underestimated due to lack of more frequent HBsAg and HBV DNA monitoring. But it is hard to perform a prospective study because an extremely long-term observation is required (at least 5–10 years). Second, there is no complete data in terms of HBV viral load prior to the immunosuppressive treatment which might be a predictor of HBsAg RS.[37] Third, the effect of sequential bDMARDs treatment on HBsAg RS could not be fully defined in this study, because of the complexity in sequential bDMARDs treatment in patients with RA .

In conclusion, anti-HBs positivity cannot confer HBV reactivation-free status if the anti-HBs levels are not high enough for patients with RA with RHB under bDMARDs treatment. Abatacept is second to rituximab with a high risk of HBV reactivation in patient with RA with RHB. A more specific HBV reactivation risk stratification and management strategy should be based on not only the types of bDMARD, but also the level of anti-HBs for patients with RA with RHB.

Twitter Chang-Youh Tsai @cytsai1240@gmail.com

Contributors 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 are accountable for all aspects of the work and will ensure questions related to the accuracy or integrity of any part of the work will be appropriately investigated and resolved. Study concept and design was by M-HC (Ming-Han) and Y-HH. Acquisition of data was done by M-HC (Ming-Han), I-CL,

M-CH, C-YT and Y-HH. M-HC (Ming-Huang) helped in analysis and interpretation of data. Drafting of manuscript was done by M-HC (Ming-Han) and Y-HH. Critical revision of the article was done by M-CH (Ming-Han). Study supervision was done by C-YT and Y-HH.

Funding This work was supported by Ministry of Science and Technology, Taiwan (grant numbers MOST 106–2314-B-010–027-MY3).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital with the reference number IRB-TPEVGH No.: 2017-09-004AC.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Ming-Han Chen http://orcid.org/0000-0001-7822-2613
Chang-Youh Tsai http://orcid.org/0000-0002-4154-4018
Yi-Hsiang Huang http://orcid.org/0000-0001-5241-5425

REFERENCES

1 World Health Organization. *Global hepatitis report, 2017*. Geneva: WHO, 2017.
2 Stanaway JD, Flaxman AD, Naghavi M, *et al*. The global burden of viral hepatitis from 1990 to 2013: findings from the global burden of disease study 2013. *Lancet* 2016;388:1081–8.
3 Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009;50:661–2.
4 Huang Y-H, Lin H-C, Lee S-D. Management of chemotherapy-induced hepatitis B virus reactivation. *J Chin Med Assoc* 2012;75:359–62.
5 Huang Y-H, Hsiao L-T, Hong Y-C, *et al*. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. *J Clin Oncol* 2013;31:2765–72.
6 Wu J-M, Huang Y-H, Lee P-C, *et al*. Fatal reactivation of hepatitis B virus in a patient who was hepatitis B surface antigen negative and core antibody positive before receiving chemotherapy for non-Hodgkin lymphoma. *J Clin Gastroenterol* 2009;43:496–8.
7 Firpi RJ, Nelson DR. Management of viral hepatitis in hematologic malignancies. *Blood Rev* 2008;22:117–26.
8 Smolen JS, Aletaha D, Barton A, *et al*. Rheumatoid arthritis. *Nat Rev Dis Primers* 2018;4:18001.
9 Nam JL, Takase-Minegishi K, Ramiro S, *et al*. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review Informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2017;76:1113–36.
10 Chen M-H, Chen M-H, Liu C-Y, *et al*. Hepatitis B virus reactivation in rheumatoid arthritis patients undergoing biologics treatment. *J Infect Dis* 2017;215:566–73.
11 Lan J-L, Chen Y-M, Hsieh T-Y, *et al*. Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. *Ann Rheum Dis* 2011;70:1719–25.
12 Oshima Y, Tsukamoto H, Tojo A. Association of hepatitis B with antirheumatic drugs: a case-control study. *Mod Rheumatol* 2013;23:694–704.
13 Lee YH, Bae S-C, Song GG. Hepatitis B virus reactivation in HBsAg-positive patients with rheumatic diseases undergoing anti-tumor necrosis factor therapy or DMARDs. *Int J Rheum Dis* 2013;16:527–31.
14 Ye H, Zhang X-wu, Mu R, *et al*. Anti-TNF therapy in patients with HBV infection--analysis of 87 patients with inflammatory arthritis. *Clin Rheumatol* 2014;33:119–23.
15 Germanidis G, Hytiroglou P, Zakalka M, *et al*. Reactivation of occult hepatitis B virus infection, following treatment of refractory rheumatoid arthritis with abatacept. *J Hepatol* 2012;56:1420–1.
16 Chen M-H, Chen M-H, Chou C-T, *et al*. Low but long-lasting risk of reversal of seroconversion in patients with rheumatoid arthritis receiving immunosuppressive therapy. *Clin Gastroenterol Hepatol* 2020;18:2573–81.
17 Perrillo RP, Gish R, Falck-Ytter YT. American gastroenterological association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015;148:221–44.
18 Reddy KR, Beavers KL, Hammond SP, *et al*. American gastroenterological association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015;148:215–9.
19 Lok ASF, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007;45:507–39.
20 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.
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 Samuel D, Bismuth A, Mathieu D, *et al*. Passive immunoprophylaxis after liver transplantation in HBsAg-positive patients. *Lancet* 1991;337:813–5.
23 Barone M, Notarnicola A, Lopalco G, *et al*. Safety of long-term biologic therapy in rheumatologic patients with a previously resolved hepatitis B viral infection. *Hepatology* 2015;62:40–6.
24 Terrault NA, Lok ASF, McMahon BJ, *et al*. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018;67:1560–99.
25 Mitroulis I, Hatzara C, Kandili A, *et al*. Long-Term safety of rituximab in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. *Ann Rheum Dis* 2013;72:308–10.
26 Varisco V, Viganò M, Batticciotto A, *et al*. Low risk of hepatitis B virus reactivation in HBsAg-negative/Anti-HBc-positive carriers receiving rituximab for rheumatoid arthritis: a retrospective multicenter Italian study. *J Rheumatol* 2016;43:869–74.
27 Tien Y-C, Yen H-H, Chiu Y-M. Incidence and clinical characteristics of hepatitis B virus reactivation in HBsAg-negative/HBcAb-positive patients receiving rituximab for rheumatoid arthritis. *Clin Exp Rheumatol* 2017;35:831–6.
28 Kuo MH, Tseng C-W, Lee C-H, *et al*. Moderate Risk of Hepatitis B Virus Reactivation in $HBsAg^{-}/HBcAb^{+}$ Carriers Receiving Rituximab for Rheumatoid Arthritis. *Sci Rep* 2020;10:2456.
29 Padovan M, Filippini M, Tincani A, *et al*. Safety of abatacept in rheumatoid arthritis with serologic evidence of past or present hepatitis B virus infection. *Arthritis Care Res* 2016;68:738–43.
30 Papalopoulos I, Fanouriakis A, Kougkas N, *et al*. Liver safety of non-tumour necrosis factor inhibitors in rheumatic patients with past hepatitis B virus infection: an observational, controlled, long-term study. *Clin Exp Rheumatol* 2018;36:102–9.
31 Yang PL, Althage A, Chung J, *et al*. Immune effectors required for hepatitis B virus clearance. *Proc Natl Acad Sci U S A* 2010;107:798–802.
32 Guidotti LG, Isogawa M, Chisari FV. Host-Virus interactions in hepatitis B virus infection. *Curr Opin Immunol* 2015;36:61–6.
33 Cao H, Zhang R, Zhang W. CTLA-4 interferes with the HBV-specific T cell immune response (Review). *Int J Mol Med* 2018;42:703–12.
34 Paul S, Dickstein A, Saxena A, *et al*. Role of surface antibody in hepatitis B reactivation in patients with resolved infection and hematologic malignancy: a meta-analysis. *Hepatology* 2017;66:379–88.
35 Liu P-C, Ssu C-T, Tsao Y-P, *et al*. Cytotoxic T lymphocyte-associated antigen-4-Ig (CTLA-4-Ig) suppresses Staphylococcus aureus-induced CD80, CD86, and pro-inflammatory cytokine expression in human B cells. *Arthritis Res Ther* 2020;22:64.
36 Jansen DTSL, Emery P, Smolen JS, *et al*. Conversion to seronegative status after abatacept treatment in patients with early and poor prognostic rheumatoid arthritis is associated with better radiographic outcomes and sustained remission: post hoc analysis of the agree study. *RMD Open* 2018;4:e000564.
37 Ji D, Cao J, Hong X, *et al*. Low incidence of hepatitis B virus reactivation during chemotherapy among diffuse large B-cell lymphoma patients who are HBsAg-negative/ HBcAb-positive: a multicenter retrospective study. *Eur J Haematol* 2010;85:243–50.

CLINICAL SCIENCE

Comparative effectiveness of two adalimumab biosimilars in 1318 real-world patients with inflammatory rheumatic disease mandated to switch from originator adalimumab: nationwide observational study emulating a randomised clinical trial

Hafsah Nabi ,[1,2] Stylianos Georgiadis ,[1] Anne Gitte Loft ,[3,4] Oliver Hendricks ,[5,6] Dorte Vendelbo Jensen,[7,8] Marlene Andersen ,[9] Stavros Chrysidis ,[10] Ada Colic ,[11] Kamilla Danebod ,[12] Mohamad Redha Hussein,[13] Maren Høgberget Kalisz ,[8] Salome Kristensen ,[14] Niels Lomborg ,[15] Natalia Manilo,[16] Heidi Lausten Munk ,[17] Jens Kristian Pedersen ,[18] Johnny Lillelund Raun,[19] Frank Mehnert ,[20] Niels Steen Krogh,[21] Merete Lund Hetland ,[1,2] Bente Glintborg [1,2]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-219951).

For numbered affiliations see end of article.

Correspondence to
Dr Hafsah Nabi, DANBIO and Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre of Head and Orthopedics, Rigshospitalet, Copenhagen, Denmark; hafsah.nabi@regionh.dk

MLH and BG shared last authorship and contributed equally to the paper.

Received 19 January 2021
Revised 9 April 2021
Accepted 10 April 2021
Published Online First 29 April 2021

To cite: Nabi H, Georgiadis S, Loft AG, *et al*. *Ann Rheum Dis* 2021;**80**:1400–1409.

ABSTRACT

Objectives In 2018, a nationwide mandatory switch from originator to biosimilar adalimumab was conducted in Denmark. The available biosimilar was GP2017 (Hyrimoz) in Eastern regions and SB5 (Imraldi) in Western regions. We aimed to assess the comparative effectiveness of GP2017 versus SB5 in patients with rheumatoid arthritis (RA)/psoriatic arthritis (PsA)/axial spondyloarthritis (AxSpA).

Methods Observational cohort study based on the DANBIO registry with geographical cluster pseudo-randomisation, analysed by emulating a randomised clinical trial. Main outcome was adjusted 1-year treatment retention (Cox regression). Furthermore, 6 months' remission rates (logistic regression), reasons for withdrawal and back-switching to originator were investigated (overall and stratified by indication).

Results Overall, of 1570 eligible patients, 1318 switched and were included (467 RA/321 PsA/530 AxSpA); 623 (47%) switched to GP2017, 695 (53%) to SB5. Baseline characteristics of the two clusters were largely similar, but some differences in registration practice were observed. The combined 1-year retention rate for the two biosimilars was 89.5%. Compared with SB5, estimated risk of withdrawal for GP2017 was lower (HR 0.60; 95% CI 0.42 to 0.86) and 6 months' remission rate was higher (OR 1.72; 95% CI 1.25 to 2.37). Stratified analyses gave similar results (statistically significant for RA). During 1 year, 8.5% and 12.9% withdrew GP2017 and SB5, respectively (primarily lack of effect and adverse events), of whom 48 patients (3.6%) back-switched.

Conclusion This head-to-head comparison of GP2017 versus SB5 following a mandatory switch from the originator indicated differences in effectiveness in routine care. This may reflect a true difference, but other explanations, for example, differences in excipients, differences between clusters and residual confounding cannot be ruled out.

Key messages

What is already known about this subject?

- Biosimilars are increasingly used in routine care of patients with inflammatory rheumatic disease. Currently, no head-to-head comparison of the different adalimumab biosimilars has been conducted.

What does this study add?

- Based on geographical cluster pseudo-randomisation, we explored outcomes in two biosimilars following a nationwide mandatory non-medical switch from originator adalimumab.
- In 1318 included switch patients, the estimated risk of withdrawal was lower and 6 months remission rate was higher for GP2017 compared with SB5. This may reflect a true difference, however other factors (differences in excipients, differences between clusters, residual confounding) cannot be ruled out.
- The 1-year treatment retention and disease remission rates for both biosimilars were high.

How might this impact on clinical practice or future developments?

- Switch outcomes following a non-medical mandatory switch in routine care for both adalimumab biosimilars were considered effective and safe.

Over the past decades, biological disease-modifying antirheumatic drugs (bDMARDs) have revolutionised the treatment of inflammatory arthritis, including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial

spondyloarthritis (AxSpA).[1] However, due to their high costs, bDMARDs pose a significant financial burden on healthcare systems around the world. The development of less expensive biosimilar drugs potentially improves accessibility of bDMARDs for patients.[1–3]

For adalimumab, several biosimilars have been approved and marketed in Europe based on results from randomised clinical trials (RCTs) comparing the effectiveness and safety of the biosimilar versus originator adalimumab.[4–10] Effectiveness of adalimumab biosimilars might potentially vary due to minor differences in molecular structures, excipients or injection devices.[11–13] RCTs are considered the gold standard for assessing efficacy and safety of medications,[14] but head-to-head comparison of biosimilars has not been conducted. Well-designed observational studies based on real-world patient data monitored in quality registries constitute a valuable alternative, especially when analysed in a way that emulates an RCT.[15 16]

In November 2018, Danish National guidelines dictated a mandatory switch from originator to biosimilar adalimumab for economic reasons (a so-called non-medical switch).[17] In Denmark, bDMARD treatment is funded by taxpayers and provided free of charge to patients. For drugs considered to be equally effective, a tendering process takes place, after which it is mandatory to prescribe the less expensive drug.[18] The expected cost reduction was 34%–49% compared with the originator (personal communication); corresponding to approximately €50 million annually in Denmark.[19] The available biosimilar was SB5 (Imraldi) in the Western regions of Denmark (Region North, Middle and South) and GP2017 (Hyrimoz) in the Eastern regions (the Capital Region and Region Zealand). Thus, the guideline provided a surrogate cluster pseudo-randomisation tool where geography rather than patient-related factors determined the choice of biosimilar.[20 21] The 'ideal hypothetical trial' that we attempted to emulate was pragmatic, in which eligible participants were patients with RA, PsA or AxSpA treated with originator adalimumab, who switched to either GP2017 or SB5 according to the national guideline.

The aim of this study was to assess the comparative effectiveness of GP2017 versus SB5 following a mandatory switch regarding 1-year treatment retention rates, 6-month disease remission rates and reasons for withdrawal. In addition, to investigate changes in disease activity 6 months prior to and after the switch, and the frequency and reasons for back-switching to originator adalimumab.

METHODS

Study design

This was a population-based, observational cohort study with surrogate cluster (ie, geographical) pseudo-randomisation. Eligible patients were identified in the Danish DANBIO quality registry. DANBIO, established in year 2000, has prospective follow-up of >95% of adults with rheumatic disease treated with bDMARDs in routine care[22] and validity is high.[23] By use of the unique Danish civil registration number that each Dane receives at birth, DANBIO data were enriched with patient-level information regarding comorbidities from The Danish National Patient Registry (DNPR), which has nearly complete data on inpatient and outpatient contacts,[24] and with information regarding vital status from The Danish Civil Registry.[25] We report our findings in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.[26]

Study population

Patients with a clinical diagnosis of RA, PsA or AxSpA, who were treated with originator adalimumab by 1 November 2018 were identified in DANBIO (figure 1).

The following patient groups were identified: (1) *Switchers*: patients, who switched from originator adalimumab to biosimilar (date of switch=baseline) between 1 November 2018 and 30 April 2019 (inclusion period). According to geographical cluster pseudo-randomisation, patients were allocated to treatment with GP2017 or SB5. (2) *Non-switchers:* patients treated with originator adalimumab by 1 November 2018 (=baseline), who did not switch to biosimilar during the inclusion period. (3) *Back-switchers:* switchers, who during 1 year's follow-up discontinued the biosimilar and resumed treatment with originator adalimumab.

Outcomes

Comparative effectiveness was assessed in patients, who switched to GP2017 versus those who switched to SB5: The adjusted comparative 1-year treatment withdrawal was the primary outcome. Key secondary outcomes were (a) the adjusted comparative 1-year treatment withdrawal stratified by indication (RA, PsA and AxSpA) and (b) disease remission at 6 months (adjusted), overall and stratified by indication. Other secondary outcomes were reasons for withdrawal across treatments.

In addition, the following outcomes were assessed: (a) changes in disease activity 6 months pre-switch versus 6 months post-switch and (b) frequency of back-switch to originator adalimumab, including patient characteristics, reasons, and time to back-switch.

Clinical variables

Clinical characteristics, disease activity and DMARD treatment history were retrieved from DANBIO (data extracted by 23 October 2020) and included the following covariates: age (years), gender (female/male), disease duration (years), body mass index, current smoker (yes/no), number of previous bDMARDs, concomitant methotrexate (MTX) (yes/no), treatment duration for originator adalimumab (years), C-reactive protein (CRP; mg/L), physician global assessment (Visual Analogue Scale (VAS), 0–100), patient reported outcomes: pain (VAS 0–100), fatigue (VAS 0–100), global assessment (VAS 0–100), functional status (Health Assessment Questionnaire (HAQ); 0–3) and Patient Acceptable Symptom State (PASS; (yes/no)).

Disease activity was assessed by, for RA and PsA: Disease Activity Score-28 (DAS28)-CRP, Clinical Disease Activity Index (CDAI); for AxSpA: Bath Ankylosing Spondylitis Indices of Disease Activity (BASDAI; 0–10) and BAS functional status (BASFI; 0–10), Ankylosing Spondylitis Disease Activity Score (ASDAS). Disease remission (yes/no) was defined as DAS28 <2.6 (RA and PsA) and ASDAS <1.3 (AxSpA).

Previous comorbidities at baseline were identified in DNPR (International Classification of Diseases, tenth revision codes, online supplemental table S1).

Switchers were followed up for 1 year. Treatment duration was calculated as the number of days that each patient maintained treatment with GP2017 or SB5, or until withdrawal (=first missed dose irrespective of reason), death or lost to follow-up, whichever came first. Treatment pauses less than 90 days (eg, due to infections or surgery) were disregarded. For treatments with no stop date, data were censored 1 year after the last visit in DANBIO. Furthermore, reasons for withdrawal (according to predefined categories in DANBIO[22]) were retrieved.

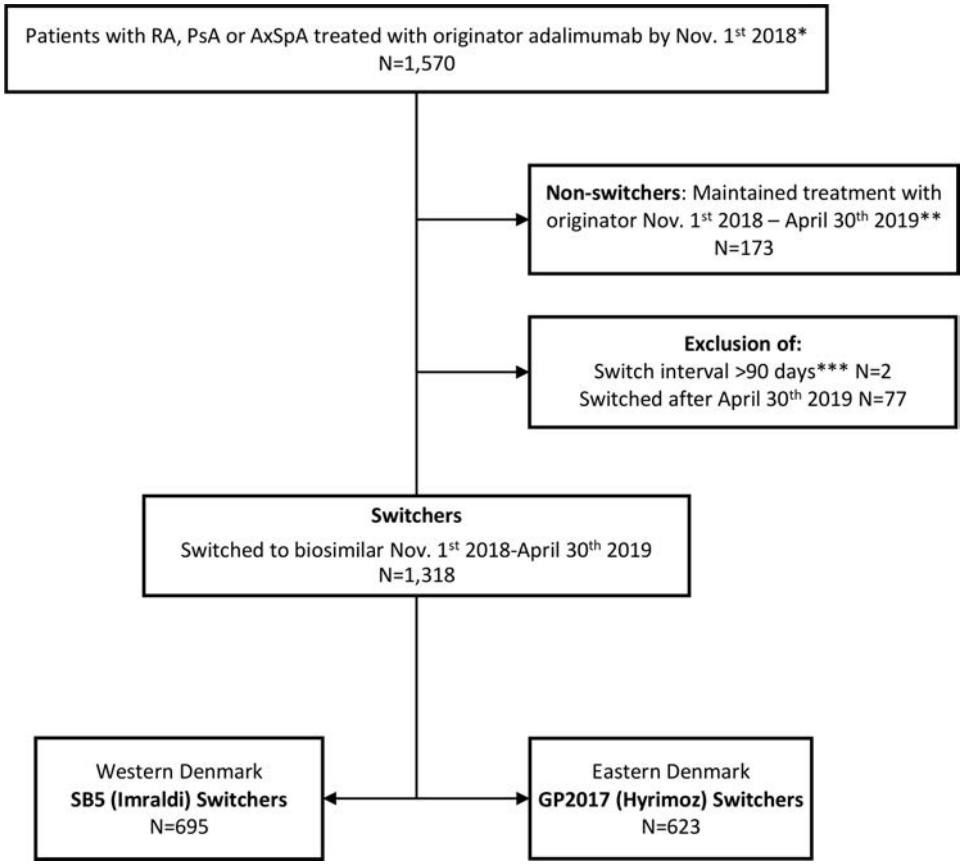


Figure 1 Flow chart of patient selection. *Minimum one visit in DANBIO after 1 November 2018 and aged ≥18 years at diagnosis. **The reasons are not registered in DANBIO. May occur in patients with complicating treatment history, comorbidities and/or prior drug intolerances or due to registration errors. ***A time gap of 0–90 days between stop of originator and start of biosimilar was allowed to comply with registration practice. AxSpA, axial spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

For back-switchers, reasons for back-switch and time to back-switch were retrieved from DANBIO. Further, disease activity at the time of biosimilar start and at the time of back-switching was compared, and changes (=delta values) were calculated in each patient.

Approvals

The study was approved by the Danish Data Protection Agency (RH-2015–209, 04145). In Denmark, registry studies require neither patient consent nor ethical approval.

Statistical analysis

All statistical analyses were done using R V.3.6.1. P values <0.05 were considered statistically significant. All analyses were conducted using an intention-to-treat approach according to a predefined statistical analysis plan. Clinical characteristics and disease activity are presented as medians (IQR) and frequencies (percentages) for continuous and categorical variables, respectively. No formal power analysis was done as all available patients in DANBIO were included in the study.

Primary and key secondary outcomes

Comparative treatment withdrawal in GP2017 versus SB5 switchers was explored with univariable and multivariable Cox proportional hazards regression analyses (overall and stratified by indication). Analyses were performed as crude, age-adjusted and gender-adjusted and fully adjusted. Adjustment was according to the following a priori defined baseline variables: age, gender, current smoker, indication, disease remission, PASS, number of previous bDMARDs, treatment duration for originator adalimumab and number of comorbidities. In stratified analysis including patients with RA, concomitant MTX was included.

Disease remission at 6 months in GP2017 versus SB5 switchers was estimated with univariable and multivariable logistic regression analyses (OR with 95% CI). Analyses were adjusted as mentioned above.

For multivariable analyses, missing baseline variables were imputed by multiple imputation using chained equations (30 imputations).[27] Proportional hazards assumption for Cox regression models was assessed in stacked imputed data sets. A rule of five events per variable was applied to avoid overfitting.

Primary and key secondary outcomes, sensitivity analyses

To mimic common inclusion and exclusion criteria in RCTs, we performed the following sensitivity analyses: S1: restricted to patients with no more than one prior bDMARD treatment in addition to originator adalimumab, and excluding patients with age >75 years, prior malignancy, >2 comorbidities and patients with RA not receiving concomitant MTX; S2: restricted to patients, who scored PASS=yes at baseline. Furthermore, Cox regression analyses of 1-year treatment withdrawal were performed, where only discontinuation due to lack of effect (LOE) or adverse events (AE) was considered an event (S3). Finally, a sensitivity analysis (S4) was performed replacing

Table 1 Clinical characteristics of patients, who switched from originator adalimumab to biosimilar GP2017 or SB5, overall and stratified by indication

	Reumatoid arthritis		Psoriatic arthritis		Axial spondyloarthritis		
	GP2017	SB5	GP2017	SB5	GP2017	SB5	Overall
Number of patients, n	214	253	148	173	261	269	1318
Female, n (%)	158 (74)	181 (72)	81 (55)	58 (34)	82 (31)	89 (33)	649 (49)
Age, years	63 (56–70)	64 (57–71)	55 (47–62)	55 (48–63)	46 (39–57)	49 (42–57)	56 (46–65)
Disease duration, years	17 (12–23)	16 (11–24)	13 (9–17)	14 (9–20)	12 (8–18)	12 (8–18)	14 (9–20)
0–5 years, n (%)	6 (3)	3 (1)	13 (9)	8 (4)	25 (10)	22 (8)	77 (6)
>5 years, n (%)	208 (97)	250 (99)	135 (91)	165 (96)	236 (90)	247 (92)	1241 (94)
BMI, kg/m^2	24.5 (22.8–28.3)	25.8 (22.9–29.4)	27.2 (24.2–30.9)	26.7 (24.2–30.5)	24.8 (22.8–27.5)	25.5 (23.1–29.1)	25.7 (23.1–29.2)
Current smoking, n (%)	52 (25)	47 (19)	37 (25)	32 (19)	77 (30)	65 (24)	310 (24)
Year of ADA treatment start							
2003–2008, n (%)	82 (39)	81 (32)	44 (30)	46 (27)	62 (24)	55 (20)	370 (28)
2009–2014, n (%)	84 (40)	151 (60)	71 (48)	97 (56)	145 (56)	160 (59)	708 (54)
2015–2019, n (%)	46 (22)	21 (8)	32 (22)	30 (17)	53 (20)	54 (20)	236 (18)
Prior ADA treatment duration, years	9 (5–12)	9 (7–11)	8 (5–10)	8 (5–10)	8 (5–10)	7 (5–10)	8 (5–10)
Concomitant MTX, n (%)	179 (84)	213 (84)	89 (60)	109 (63)	72 (28)	55 (20)	717 (54)
Prior bDMARD treatments, n (%)							
Only adalimumab originator	87 (41)	163 (64)	90 (61)	130 (75)	141 (54)	167 (62)	778 (59)
1	81 (38)	69 (27)	41 (28)	28 (16)	82 (31)	54 (20)	355 (27)
≥2	46 (21)	21 (8)	17 (11)	15 (9)	38 (15)	49 (18)	185 (14)
Visits during 1-year follow-up	2 (1–3)	2 (2–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
Disease activity							
In DAS28/ASDAS remission*, n (%)	87 (67)	175 (80)	66 (76)	109 (76)	66 (37)	89 (42)	592 (61)
In CDAI/ASDAS remission†, n (%)	39 (30)	94 (44)	30 (32)	74 (50)	66 (37)	89 (42)	392 (40)
CRP, mg/L	2 (1–4)	2 (1–4)	2 (1–3)	2 (1–4)	2 (1–3)	2 (1–4)	2 (1–4)
DAS28	2.3 (1.7–2.8)	2.0 (1.5–2.5)	2.1 (1.6–2.6)	1.9 (1.6–2.6)	–	–	–
CDAI	5.1 (2.1–8.3)	3.6 (1.5–6.9)	4.3 (2.2–7.6)	2.8 (1.2–7.3)	–	–	–
BASDAI, cm	–	–	–	–	2.5 (1.0–4.7)	2.7 (1.2–4.7)	–
BASFI	–	–	–	–	2.1 (0.8–4.0)	2.1 (0.8–4.5)	–
ASDAS	–	–	–	–	1.7 (1.0–2.5)	1.6 (1.0–2.5)	–
Physician global VAS, mm	5 (2–11)	4 (1–6)	7 (3–11)	4 (1–8)	7 (3–16)	4 (1–8)	5 (2–9)
Patient pain VAS, mm	27 (12–49)	22 (8–46)	28 (14–48)	19 (8–52)	23 (8–47)	22 (8–45)	24 (8–48)
Patient fatigue VAS, mm	44 (20–66)	37 (14–63)	39 (24–64)	34 (17–64)	33 (14–65)	39 (14–70)	37 (16–66)
Patient global VAS, mm	30 (15–62)	27 (9–53)	30 (12–56)	20 (9–56)	23 (8–49)	24 (9–53)	25 (10–54)
HAQ	0.6 (0.2–1.1)	0.5 (0.1–1.1)	0.5 (0.1–0.9)	0.4 (0.0–0.9)	0.2 (0.0–0.6)	0.2 (0.0–0.8)	0.4 (0.0–0.9)
PASS yes, n (%)	114 (80)	181 (84)	71 (72)	120 (78)	165 (78)	174 (79)	825 (79)
Previous comorbidities‡							
Cancer, n (%)	14 (7)	5 (2)	4 (3)	5 (3)	5 (2)	5 (2)	38 (3)
Hospitalised Infection, n (%)	62 (29)	66 (26)	48 (33)	41 (24)	66 (26)	50 (19)	333 (26)
Knee/hip prosthesis, n (%)	27 (13)	25 (10)	4 (3)	4 (2)	9 (4)	5 (2)	74 (6)
Pulmonary disease, n (%)	13 (6)	16 (6)	3 (2)	11 (6)	13 (5)	19 (7)	75 (6)
Diabetes, n (%)	13 (6)	16 (6)	11 (8)	9 (5)	13 (5)	8 (3)	70 (5)
Myocardial infarction, n (%)	5 (2)	8 (3)	3 (2)	2 (1)	3 (1)	5 (2)	26 (2)
Chronic kidney disease, n (%)	6 (3)	4 (2)	2 (1)	2 (1)	4 (2)	5 (2)	23 (2)
Number of comorbidities							
0, n (%)	119 (56)	140 (56)	86 (59)	110 (65)	161 (63)	181 (69)	797 (62)
≥1, n (%)	93 (44)	110 (44)	59 (41)	60 (35)	94 (37)	82 (31)	498 (38)

Numbers are median (IQR) unless otherwise stated. Baseline is in time-window −175 days to +6 days according to switch date.
*Remission defined as DAS28 <2.6 (RA, PsA), ASDAS <1.3 (AxSpA).
†CDAI remission defined as <2.9 (RA, PsA).
‡0–10 years prior to baseline and 0-ever for cancer.
ADA, originator adalimumab; ASDAS, Ankylosing Spondylitis Disease Activity Score; AxSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Indices of Disease Activity (0–10); BASFI, BAS functional status (0–10); bDMARD, biological disease-modifying antirheumatic drugs; BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease activity score (four variables); HAQ, Functional status (Health Assessment Questionnaire) 0–3; MTX, methotrexate; PASS, Patient Acceptable Symptom State (yes/no); patient pain (VAS 0–100), fatigue (VAS 0–100), patient global assessment (VAS 0–100) and physician global VAS (0–100); ;PsA, psoriatic arthritis; RA, rheumatoid arthritis; VAS, Visual Analogue Scale.

DAS28 remission with CDAI remission (CDAI <2.9) for patients with RA and PsA.

RESULTS

Of 1570 patients treated with originator adalimumab by 1 November 2018, 1318 (84%) switched to GP2017 (623, 47%) or SB5 (695, 53%) before 30 April 2019 and were included (table 1, figure 1). All patients were assigned the biosimilar treatment in compliance with the guideline, that is, according to their geographical region. In general, the patients had established disease with median 8 years of originator adalimumab treatment. At baseline, the majority (61%) of the patients were in remission. A total of 173 patients (11%) did not switch and were excluded (baseline characteristics in online supplemental table S3).

Table 2 One-year comparative treatment withdrawal in GP2017 versus SB5 for overall switch cohort and stratified by indication, results of crude and adjusted Cox regression analyses

	Overall cohort		RA		PsA		AxSpA	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Main analysis	n=1318		n=467		n=321		n=530	
Unadjusted	0.69 (0.49 to 0.97)	0.034	0.50 (0.28 to 0.91)	0.023	1.00 (0.49 to 2.03)	0.991	0.74 (0.42 to 1.32)	0.305
Age and gender adjusted	0.66 (0.47 to 0.94)	0.02	0.50 (0.28 to 0.90)	0.021	0.97 (0.46 to 2.02)	0.927	0.75 (0.42 to 1.33)	0.317
Fully adjusted*	0.60 (0.42 to 0.86)	0.005	0.48 (0.26 to 0.88)	0.019	NA	NA	0.68 (0.38 to 1.22)	0.187
Sensitivity analysis S1†	n=982		n=283		n=274		n=425	
Unadjusted	0.66 (0.43 to 1.02)	0.06	0.61 (0.28 to 1.33)	0.208	1.14 (0.48 to 2.71)	0.761	0.51 (0.25 to 1.05)	0.068
Age and gender adjusted	0.64 (0.41 to 0.99)	0.046	0.61 (0.28 to 1.34)	0.209	1.08 (0.44 to 2.63)	0.857	0.48 (0.23 to 0.99)	0.048
Fully adjusted*	0.59 (0.37 to 0.92)	0.021	NA	NA	NA	NA	NA	NA
Sensitivity analysis S2:‡	n=825		n=295		n=191		n=339	
Unadjusted	0.68 (0.43 to 1.08)	0.103	0.65 (0.31 to 1.35)	0.24	1.10 (0.39 to 3.08)	0.846	0.58 (0.26 to 1.30)	0.176
Age and gender adjusted	0.69 (0.43 to 1.09)	0.111	0.66 (0.32 to 1.37)	0.256	1.16 (0.40 to 3.34)	0.764	0.56 (0.25 to 1.28)	0.163
Fully adjusted*	0.63 (0.40 to 1.02)	0.058	NA	NA	NA	NA	NA	NA
Sensitivity analysis S3§	n=1318		n=467		n=321		n=530	
Unadjusted	0.73 (0.50 to 1.08)	0.117	0.58 (0.30 to 1.14)	0.111	1.02 (0.45 to 2.31)	0.954	0.74 (0.40 to 1.38)	0.335
Age and gender adjusted	0.70 (0.48 to 1.04)	0.074	0.57 (0.29 to 1.12)	0.098	1.02 (0.44 to 2.37)	0.952	0.73 (0.39 to 1.38)	0.336
Fully adjusted*	0.64 (0.43 to 0.94)	0.024	NA	NA	NA	NA	NA	NA
Sensitivity analysis S4¶	n=1318		n=467		n=321		n=530	
Unadjusted	0.69 (0.49 to 0.97)	0.034	0.50 (0.28 to 0.91)	0.023	1.00 (0.49 to 2.03)	0.991	0.74 (0.42 to 1.32)	0.305
Age and gender adjusted	0.66 (0.47 to 0.94)	0.02	0.50 (0.28 to 0.90)	0.021	0.97 (0.46 to 2.02)	0.927	0.75 (0.42 to 1.33)	0.317
Fully adjusted*	0.59 (0.41 to 0.84)	0.004	0.47 (0.26 to 0.86)	0.016	NA	NA	0.68 (0.38 to 1.22)	0.187

*Adjusted for baseline age, gender, current smoking, indication (only for overall switch cohort), baseline disease remission (Disease Activity Score-28/Ankylosing Spondylitis Disease Activity Score), PASS, number of previous biological disease-modifying antirheumatic drugs (bDMARDs), treatment duration for originator adalimumab treatment, number of comorbidities (0 and ≥1). For patients with RA: Also baseline concomitant methotrexate (MTX). NA: Analyses where assumptions of proportional hazards or the 'rule of 5' were not met (see methods for details).
†S1: Randomised clinical trial inclusion and exclusion criteria: inclusion of patients with no more than one prior bDMARD treatment apart from originator adalimumab. Exclusion of patients >75 years, prior malignancy, >2 comorbidities and patients with RA not receiving concomitant MTX.
‡S2: Restricted to patients, who scored PASS=yes at baseline.
§S3: Only discontinuation due to lack of effect and/or adverse events was considered an event.
¶S4: Similar to the main analysis except baseline disease remission defined by Clinical Disease Activity Index <2.9 (RA and PsA).
AxSpA, axial spondyloarthritis; PASS, Patient Acceptable Symptom State; ; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

Baseline characteristics of switchers stratified by indication

Compared with patients who switched to SB5, those who switched to GP2017 had similar age, gender (mainly RA and AxSpA), disease duration, concomitant use of MTX and comorbid burden (table 1), but appeared to have higher disease activity and patient reported outcomes (mainly RA and PsA), more prior bDMARD treatments and more were current smokers. The number of follow-up visits during the first year was similar for both groups (table 1, online supplemental table S2).

Comparative 1-year treatment withdrawal

For all switchers, the combined 1-year crude treatment retention rate was 89.5% (Kaplan-Meier estimation). For GP2017, the overall estimated risk of withdrawal was lower than for SB5 (HR 0.60; 95% CI 0.42 to 0.86) (multivariable Cox regression analysis, fully adjusted, table 2, figure 2). Stratified by indication, similar results were found for patients with RA (HR 0.50; 95% CI 0.28 to 0.90), whereas for PsA and AxSpA the results did not reach statistical significance: HR 0.97 (95% CI 0.46 to 2.02) and HR 0.75 (95% CI 0.42 to 1.33), respectively (age and gender adjusted, table 2).

Remission rates at 6 months

At 6 months, 56% of switchers were in DAS28/ASDAS remission. The odds of being in remission were higher for GP2017 compared with SB5 (OR 1.72; 95% CI 1.25 to 2.37). Similar results were found when stratified by indication (logistic regression analysis, fully adjusted, table 3), but only statistically significant for patients with RA (OR 1.81; 95% CI 1.07 to 3.06).

Reasons for withdrawal

During 1-year follow-up, 53 patients (8.5%) withdrew from treatment with GP2017 and 90 (12.9%) from SB5, respectively, mainly due to LOE and AEs (table 4, online supplemental table S4). Among SB5 switchers, more patients withdrew due to remission, loss to follow-up and other reasons, including change of hospital.

Compared with the overall switch population, patients who withdrew biosimilar treatment were more often women, had received fewer prior bDMARD treatments and tended to have higher disease activity at baseline both regarding subjective and objective measures (online supplemental table S4).

Sensitivity analyses

In sensitivity analysis S1 applying strict inclusion/exclusion criteria, the estimated risk of withdrawal for GP2017 switchers (with SB5 as the reference) showed results similar to the main analysis (HR 0.59; 95% CI 0.37 to 0.92). The estimates remained similar across all sensitivity analyses with HR ranging from 0.59 to 0.64 (fully adjusted, table 2). Stratified by indication, age and gender adjusted estimates had wide CIs, which included 1.

Sensitivity analyses for remission at 6 months demonstrated estimates largely similar to the main analyses (table 3). When

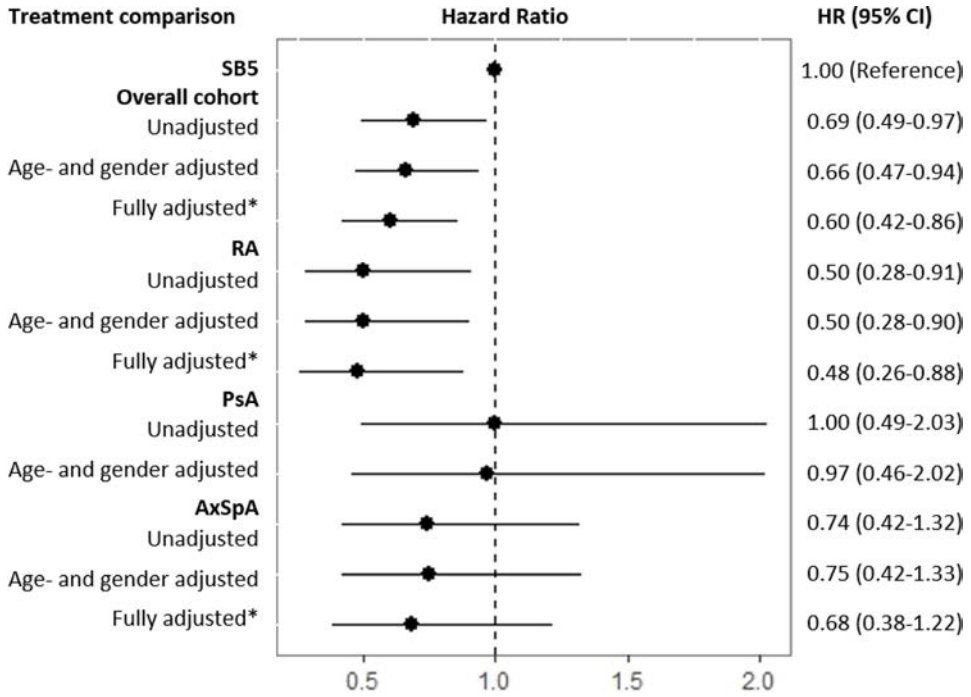


Figure 2 Comparative 1-year treatment withdrawal in GP2017 versus SB5 switchers for overall switch cohort and stratified by indication. Results of crude and adjusted Cox regression analyses. *Adjusted for baseline age, gender, current smoking, indication (only for overall switch cohort), baseline Disease Activity Score-28/Ankylosing Spondylitis Disease Activity Score remission, Patient Acceptable Symptom State, number of previous biological disease-modifying antirheumatic drugs, treatment duration for originator adalimumab treatment, number of comorbidities (0 and ≥1). For patients with RA: Also baseline concomitant methotrexate. AxSpA, axial spondylarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

replacing DAS28 remission with CDAI remission (sensitivity analysis S4), the estimates were lower. Baseline characteristics for patients included in the sensitivity analyses are shown in online supplemental tables S5 and S6.

Disease activity 6 months pre-switch and post-switch

For both GP2017 and SB5, changes in disease activity 6 months pre-switch and post-switch in individual patients were close to zero for all measures (eg, DAS28, CDAI, VAS scores) (table 5).

Back-switchers to originator adalimumab

Among patients, who withdrew GP2017 or SB5 during follow-up, 48 switched back to originator adalimumab (=back-switchers), 52 commenced treatment with another bDMARD, 1 died, 5 were lost to follow-up and 37 did not restart bDMARDs. Treatment duration before back-switching to originator was median 174 days (IQR 101–250) (online supplemental table S7). Back-switch was mainly due to LOE (54%) and AE (27%). Back-switchers were mostly women, had RA and >50% had ≥3 prior bDMARD treatments (online supplemental table S7).

At the time of back-switch, fewer patients were in remission (58% vs 33%) or scored PASS=yes (82% vs 32%), respectively, compared with when they switched, whereas changes in CRP and HAQ were close to zero (online supplemental table S7).

DISCUSSION

In this nationwide study, we investigated 1-year comparative effectiveness of two adalimumab biosimilars (GP2017 vs SB5) in >1300 real-world patients with arthritis, who were mandated to switch from originator adalimumab. We emulated an RCT comparing these two active treatments using geographical residence (GP2017 in East and SB5 in West Denmark) as the surrogate randomisation tool based on national treatment guidelines.

Knowledge regarding non-medical switching mainly stems from phase III extension of RCTs where patients, who initially received the originator drug were randomised to either maintain treatment or switch to the biosimilar drug.[4 5 7 8 10] These studies included patients who are highly selected and often bDMARD naïve, and did not study patients with PsA or AxSpA.[4 5 7 8 10] Since no RCT with head-to-head comparison of biosimilars has been performed, post-marketing registry studies of real-life patients may help fill the knowledge gap and provide important evidence for clinical decision-making. The few minor observational studies currently available, mainly conducted in patients with inflammatory bowel disease, have shown stable disease activity following non-medical switch to biosimilar adalimumab.[28 29]

Strengths of the current study include the nationwide prospective follow-up, high data completeness and high compliance to the guideline with only 11% non-switchers. The cluster pseudo-randomisation was successful, since all patients were assigned biosimilar treatment according to their geographical region, and the number of patients in the two treatment groups was comparable.

We found lower risk of withdrawal and higher remission rates for GP2017 compared with SB5. The difference, which was most consistent in patients with RA, was observed also after adjustment for a large number of baseline variables, and in both the main analyses and in the sensitivity analyses. Due to the observational nature of the study, the difference can not necessarily be attributed to the drug per se, and potential confounders and biases need to be addressed.

First, differences in devices, injection site reactions or differences in buffers are examples of factors, which may have affected drug retention and patient satisfaction. It appeared that itching and burning at the injection site were more often reported in SB5-treated patients, which could be speculated to arise from

Table 3 Disease remission at 6 months in GP2017 switchers with SB5 as reference for overall switch cohort and stratified by indication, results of logistic regression analyses

	Overall cohort		RA		PsA		AxSpA	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Main analysis	n=1110		n=401		n=263		n=446	
Unadjusted	1.12 (0.88 to 1.42)	0.369	1.22 (0.78 to 1.88)	0.383	1.02 (0.57 to 1.79)	0.958	1.25 (0.85 to 1.86)	0.261
Age and gender adjusted	1.14 (0.89 to 1.45)	0.294	1.23 (0.79 to 1.92)	0.352	1.32 (0.72 to 2.41)	0.373	1.21 (0.81 to 1.81)	0.356
Fully adjusted*	1.72 (1.25 to 2.37)	0.001	1.81 (1.07 to 3.06)	0.027	1.79 (0.88 to 3.66)	0.108	1.87 (1.04 to 3.34)	0.036
Sensitivity analysis S1†	n=812		n=242		n=214		n=356	
Unadjusted	1.00 (0.75 to 1.32)	0.982	1.08 (0.61 to 1.91)	0.801	0.89 (0.46 to 1.70)	0.721	1.29 (0.84 to 1.98)	0.252
Age and gender adjusted	1.03 (0.78 to 1.37)	0.819	1.06 (0.59 to 1.89)	0.844	1.06 (0.54 to 2.08)	0.863	1.22 (0.78 to 1.89)	0.38
Fully adjusted*	1.59 (1.09 to 2.32)	0.016	1.65 (0.80 to 3.40)	0.173	1.78 (0.78 to 4.02)	0.167	1.77 (0.95 to 3.30)	0.07
Sensitivity analysis S2‡	n=709		n=261		n=161		n=287	
Unadjusted	1.14 (0.84 to 1.56)	0.399	1.41 (0.78 to 2.56)	0.255	1.50 (0.64 to 3.51)	0.353	1.39 (0.86 to 2.23)	0.179
Age and gender adjusted	1.16 (0.85 to 1.59)	0.351	1.43 (0.79 to 2.60)	0.241	2.05 (0.82 to 5.09)	0.121	1.31 (0.80 to 2.15)	0.283
Fully adjusted*	1.87 (1.23 to 2.85)	0.003	1.77 (0.91 to 3.44)	0.09	NA	NA	1.63 (0.81 to 3.26)	0.169
Sensitivity analysis S4§	n=1110		n=401		n=263		n=446	
Unadjusted	0.92 (0.72 to 1.18)	0.531	0.88 (0.58 to 1.32)	0.527	0.63 (0.38 to 1.03)	0.063	1.25 (0.85 to 1.86)	0.261
Age and gender adjusted	0.93 (0.73 to 1.19)	0.575	0.86 (0.57 to 1.31)	0.485	0.79 (0.47 to 1.34)	0.388	1.21 (0.81 to 1.81)	0.356
Fully adjusted*	1.49 (1.07 to 2.08)	0.019	1.41 (0.81 to 2.46)	0.22	1.34 (0.67 to 2.67)	0.408	1.87 (1.04 to 3.34)	0.036

Disease remission defined as Disease Activity Score-28 <2.6 (RA and PsA) and Ankylosing Spondylitis Disease Activity Score <1.3 (AxSpA). Time-windows applied for data capture regarding disease activity at 6 months were +7 days to +365 days after switch date.
For patients with missing data on disease remission at 6 months, the following assumptions were made as part of an approximated intention-to-treat analysis: (1) patients, who had withdrawn treatment (0–6 months) due to lack of effect were classified as being not in remission, (2) patients, who had withdrawn (0–6 months) due to remission were classified as being in remission, (3) patients, who were still being treated but had >1 swollen joint at 6 months were classified as being not in remission, (4) patients who were still being treated, but had patient global score >30 mm were classified as being not in remission and (5) patients who still had missing data on disease remission were classified as being (a) excluded, with additional sensitivity analyses, (b) in remission (best case scenario) and (c) not in remission (worst case scenario). Analyses where the 'rule of 5' was not met are indicated with NA in the results.
*Adjusted for baseline age, gender, current smoking, indication (only for overall switch cohort), baseline disease remission, PASS, number of previous biological disease-modifying antirheumatic drugs (bDMARDs), treatment duration for originator adalimumab treatment, number of comorbidities (0 and ≥1). For patients with RA: Also baseline concomitant methotrexate (MTX).
†S1: Randomised clinical trial inclusion and exclusion criteria: inclusion of patients with no more than one prior bDMARD treatment apart from originator adalimumab. Exclusion of patients >75 years, prior malignancy, >2 comorbidities and patients with RA not receiving concomitant MTX.
‡S2: Restricted to patients, who scored PASS=yes at baseline.
§S4: Similar to the main analysis except disease remission defined by Clinical Disease Activity Index <2.9 (RA and PsA).
AxSpA, axial spondyloarthritis; PASS, Patient Acceptable Symptom State; ; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

differences in buffers (citrate or phosphate) (personal communication).[30] Unfortunately, we do not have data to further explore this.

Second, geographical clusters (in this study the Western and Eastern regions of Denmark) are never exactly alike, which is a known challenge in the interpretation of cluster-randomised studies.[31] This raises the question whether the differences in effectiveness that we found between GP2017 and SB5 relate to the individual patients or to the geographical region. More patients in the Western regions (ie, treated with SB5) were lost to follow-up or withdrew due to other reasons than LOE and AE, including change of hospital during follow-up. Although the number of follow-up visits were similar for Eastern and Western regions, follow-up bias or registration bias may have been present.

Table 4 Main reasons for withdrawal during 1-year follow-up according to treatment

Reason, n (% of withdrawals)	GP2017	SB5
Lack of effect, n (%)	26 (49)	38 (42)
Adverse events, n (%)	15 (28)	21 (23)
Cancer, n (%)	1 (2)	3 (3)
Remission, n (%)	2 (4)	6 (7)
Pregnancy, n (%)	0 (0)	0 (0)
Infection, n (%)	1 (2)	0 (0)
Death, n (%)	1 (2)	0 (0)
Loss to follow-up, n (%)	0 (0)	5 (6)
Surgery, n (%)	0 (0)	0 (0)
Other, n (%)	3 (6)	7 (8)
Several reasons, n (%)	3 (6)	7 (8)
Not stated, n (%)	1 (2)	3 (3)
Total	53 (100)	90 (100)

Thirdly, confounding by indication was reduced, since the choice of biosimilar was based on geographical region, not on patient-related factors. Although baseline patient characteristics were well balanced in our study, some noteworthy differences were found. GP2017 switchers appeared to have higher disease activity, more frequently to be smokers and have failed more prior bDMARD treatments, which we adjusted for in the multivariable analyses. However, we cannot exclude residual confounding, for example, socioeconomic factors or other patient characteristics that were not available.[32]

Finally, although this study was a mandated nationwide switch, regional differences in the transition and communication strategy with patients cannot be excluded. The information was mainly given by nurses in the outpatient clinics, and no specific patient-material was developed. Patients included in the study had been treated with originator adalimumab for median 8 years. They were generally satisfied with the originator as illustrated by high remission rate and high patient satisfaction (PASS). Neither patients, nor physicians were blinded for the switch, and patient-related and/or physician-related factors may

Table 5 Disease activity 6 months prior to, at time of switch and 6 months after switch, stratified by indication and by biosimilar adalimumab

	GP2017 switch patients					SB5 switch patients				
	6 months pre-switch	Switch (baseline)	6 months post-switch	Pre-switch (delta values)*	Post-switch (delta values)*	6 months pre-switch	Switch (baseline)	6 months post-switch	Pre-switch (delta values)*	Post-switch (delta values)*
Rheumatoid Arthritis	**n=214**					**n=253**				
DAS28	2.1 (1.7 to 2.7)	2.3 (1.7 to 2.8)	2.0 (1.6 to 2.6)	0.0 (–0.2 to 0.4)	–0.0 (–0.5 to 0.3)	2.0 (1.5 to 2.5)	2.0 (1.5 to 2.5)	2.0 (1.6 to 2.8)	–0.1 (–0.4 to 0.2)	0.1 (–0.2 to 0.5)
HAQ (0–3)	0.6 (0.1 to 1.1)	0.6 (0.2 to 1.1)	0.6 (0.2 to 1.1)	0.0 (–0.1 to 0.1)	0.0 (–0.1 to 0.1)	0.6 (0.1 to 1.2)	0.5 (0.1 to 1.1)	0.6 (0.1 to 1.2)	0.0 (–0.1 to 0.1)	0.0 (–0.1 to 0.1)
CRP, mg/L	2 (1 to 4)	2 (1 to 4)	3 (1 to 4)	0.0 (–1.0 to 0.1)	0.0 (–1.0 to 1.0)	2 (1 to 4)	2 (1 to 4)	3 (1 to 5)	0.0 (–1.0 to 1.0)	0.0 (–1.0 to 1.8)
CDAI	5.1 (2.1 to 8.0)	5.1 (2.1 to 8.3)	4.4 (2.1 to 7.7)	0.0 (–1.4 to 1.8)	0.0 (–1.6 to 1.5)	3.7 (1.6 to 6.8)	3.6 (1.5 to 6.9)	4.2 (1.4 to 8.1)	–0.2 (–1.6 to 1.0)	0.0 (–1.0 to 2.0)
VAS patient global, mm	32 (13 to 55)	30 (15 to 62)	33 (13 to 61)	0 (–9 to 9)	0 (–8 to 10)	29 (10 to 53)	27 (9 to 53)	31 (10 to 54)	0 (–8 to 6)	0 (–8 to 11)
VAS pain, mm	27 (11 to 48)	27 (12 to 49)	31 (12 to 53)	0 (–7 to 5)	0 (–8 to 9)	26 (9 to 47)	22 (8 to 46)	27 (8 to 50)	0 (–9 to 6)	1 (–7 to 9)
VAS fatigue, mm	46 (20 to 66)	44 (20 to 68)	49 (20 to 70)	–1 (–12 to 8)	2 (–10 to 13)	37 (18 to 62)	37 (14 to 63)	38 (16 to 64)	0 (–7 to 7)	0 (–9 to 11)
Psoriatic Arthritis	**n=148**					**n=173**				
DAS28	2.0 (1.6 to 2.6)	2.1 (1.6 to 2.6)	1.9 (1.5 to 2.6)	0.0 (–0.2 to 0.3)	0.0 (–0.4 to 0.2)	1.9 (1.5 to 2.7)	1.9 (1.6 to 2.6)	1.8 (1.5 to 2.6)	0.0 (–0.3 to 0.4)	0.0 (–0.3 to 0.4)
HAQ (0–3)	0.5 (0.0 to 0.9)	0.5 (0.1 to 0.9)	0.5 (0.0 to 1.0)	0.0 (–0.1 to 0.1)	0.0 (–0.1 to 0.1)	0.2 (0.0 to 0.9)	0.4 (0.0 to 0.9)	0.2 (0.0 to 0.9)	0.0 (–0.1 to 0.1)	0.0 (–0.1 to 0.1)
CRP, mg/L	2 (1 to 3)	2 (1 to 3)	2 (1 to 3)	0.0 (0.0 to 0.9)	0.0 (0.0 to 1.0)	2 (1 to 4)	2 (1 to 4)	2 (1 to 4)	0.0 (–1.5 to 1.0)	0.0 (–1.0 to 1.3)
CDAI	4.2 (2.1 to 7.8)	4.3 (2.2 to 7.6)	3.8 (2.1 to 6.9)	0.1 (–1.6 to 1.5)	0.3 (–2.3 to 1.5)	3.2 (1.2 to 6.8)	2.8 (1.2 to 7.3)	2.8 (1.4 to 7.0)	0.0 (–1.1 to 1.6)	0.1 (–0.8 to 1.6)
VAS patient global, mm	26 (14 to 57)	30 (12 to 56)	28 (12 to 55)	0 (–9 to 9)	2 (–5 to 9)	20 (9 to 54)	20 (9 to 56)	20 (9 to 52)	0 (–6 to 6)	0 (–5 to 10)
VAS pain, mm	26 (7 to 51)	28 (14 to 48)	26 (10 to 44)	0 (–6 to 6)	0 (–5 to 9)	18 (7 to 49)	19 (8 to 52)	20 (8 to 49)	–1 (–7 to 8)	0 (–5 to 6)
VAS fatigue, mm	48 (27 to 67)	39 (24 to 64)	42 (21 to 62)	–4 (–13 to 7)	0 (–8 to 12)	32 (12 to 61)	34 (17 to 64)	28 (14 to 61)	0 (–9 to 9)	0 (–6 to 9)
Axial Spondyloarthritis	**n=261**					**n=269**				
BASDAI, cm	2.2 (1.0 to 4.9)	2.5 (1.0 to 4.6)	2.5 (1.1 to 4.5)	0.0 (–0.8 to 0.5)	0.0 (–0.5 to 0.8)	2.4 (0.9 to 4.2)	2.7 (1.2 to 4.7)	2.5 (1.1 to 4.9)	0.2 (–0.5 to 0.8)	0.0 (–0.6 to 0.8)
ASDAS	1.6 (1.1 to 2.6)	1.7 (1.0 to 2.5)	1.6 (1.0 to 2.5)	0.0 (–0.6 to 0.3)	–0.0 (–0.4 to 0.3)	1.6 (0.9 to 2.4)	1.6 (1.0 to 2.5)	1.7 (1.1 to 2.6)	0.0 (–0.4 to 0.5)	0.1 (–0.2 to 0.6)
CRP, mg/L	2 (1 to 4)	2 (1 to 3)	2 (1 to 4)	0.0 (–1.6 to 0.1)	0.0 (–1.0 to 0.1)	2 (1 to 4)	2 (1 to 4)	3 (1 to 4)	0.0 (–1.0 to 1.0)	0.0 (–0.6 to 1.3)
VAS patient global, mm	22 (11 to 50)	23 (8 to 49)	26 (9 to 50)	0 (–6 to 8)	0 (–7 to 9)	22 (8 to 46)	24 (9 to 53)	25 (8 to 56)	2 (–6 to 10)	2 (–7 to 10)
VAS pain, mm	20 (9 to 42)	23 (8 to 47)	21 (8 to 46)	0 (–4 to 8)	0 (–7 to 8)	19 (7 to 41)	22 (8 to 45)	23 (8 to 45)	0 (–7 to 9)	1 (–7 to 9)
VAS fatigue, mm	36 (14 to 61)	33 (14 to 65)	36 (14 to 60)	0 (–8 to 10)	0 (–10 to 10)	32 (15 to 64)	39 (13 to 70)	41 (16 to 67)	0 (–6 to 14)	1 (–7 to 9)

Numbers are medians (IQR) unless otherwise stated.

*Delta values are changes in disease activity at time of switch minus 6 months before switch (pre-switch), and 6 months after switch minus at time of switch (post-switch) in individual patients. Time windows pre-switch: 6 months' window: –365 days to –176 days before start of biosimilar. Time windows switch: –175 days to +6 days after start of biosimilar. Time window post-switch: 6 months' window: +7 days to +365 days after start of biosimilar. In case of several visits within a given time window, the visit closest to the given time point was selected If a patient had no registrations, data will be registered as missing for that visit. For patients who withdrew <6 months post-switch, data from latest registered visit after baseline will be carried forward.

ASDAS, Ankylosing Spondylitis Disease Activity Score; AxSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Indices of Disease Activity (0–10); BASFI, BAS functional status (0–10); CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score (four variables); HAQ, functional status (Health Assessment Questionnaire) 0–3; MTX, methotrexate; PASS, Patient Acceptable Symptom State (yes/no); patient pain (VAS 0–100), fatigue (VAS 0–100), patient global assessment (VAS 0–100) and physician global VAS (VAS, 0–100); PsA, psoriatic arthritis; RA, rheumatoid arthritis; VAS, Visual Analogue Scale.

have affected outcomes. Thus, negative expectations towards the biosimilar (the so-called nocebo effect) and/or incorrect causal attributions, may potentially have affected patients' experience and consequently outcomes.[30 33 34]

The combined 1-year retention rate for the two biosimilars was high with 9 in 10 patients maintaining treatment, and the remission rate at 6 months remained largely unchanged. In individual patients, changes in disease activity pre-switch and post-switch were negligible for both GP2017 and SB5. The main reasons for withdrawal were LOE and AE, which is in agreement with what has been reported for the originator drug.[4 5 7 8 10]

The use of biosimilars including switch procedures in routine care varies substantially between countries.[35–37] In Denmark, bDMARDs are provided free-of-cost by public hospital owners via a tax-based system, and mandated switch procedures are implemented after marketing of less expensive biosimilars.[38 39] Previous experiences with non-medical switching in routine care have been positive[34 40 41] in rheumatological patients treated with infliximab and etanercept. Thus, we have previously reported that 78%–84% of patients maintained treatment 1 year after switching, similar to that of a historic cohort,[38 39] which is of magnitude similar to that of the current study. Results from a recent Danish study have shown that Denmark has benefitted from substantial price reductions after patent expiration of the originator adalimumab.[18] Only few patients (4%) back-switched to the originator adalimumab during follow-up. At the time of back-switch, patients had higher patient-reported outcomes, whereas the more objective markers remained unchanged (swollen joint count, CRP), suggesting that subjective health experiences influenced the perception of treatment outcomes and AEs, in line with results from our previous study on etanercept switchers.[38]

In conclusion, we emulated an RCT by using a surrogate randomisation tool (geographical region) in this observational study of >1300 patients, who conducted a mandatory switch from originator adalimumab to one of two biosimilars according to a national guideline. This allowed us to directly compare two adalimumab biosimilars, GP2017 and SB5. Our results indicated a difference between the two biosimilars. This may be a true difference between the active drugs, but other explanations, for example, differences in excipients, differences between clusters and residual confounding cannot be ruled out.

Author affiliations
[1]DANBIO and Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre of Head and Orthopedics, Rigshospitalet, Copenhagen, Denmark
[2]Department of Clinical Medicine, University of Copenhagen Faculty of Health and Medical Sciences, Copenhagen, Denmark
[3]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark
[4]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
[5]Danish Hospital for Rheumatic Diseases, University Hospital of Southern Denmark, Sønderborg, Denmark
[6]Department of Regional Health Research, University of Southern Denmark, Odense, Denmark
[7]Department of Internal Medicine, Rønne Hospital, Rønne, Denmark
[8]Department of Rheumatology, Gentofte and Herlev Hospital, Copenhagen University Hospital, Gentofte, Denmark
[9]Department of Rheumatology, North Denmark Regional Hospital, Hjørring, Denmark
[10]Department of Rheumatology, Esbjerg Hospital, Esbjerg, Denmark
[11]Department of Rheumatology, Zealand University Hospital, Køge, Denmark
[12]Department of Rheumatology, Center for Rheumatology and Spine Diseases, Centre of Head and Orthopedics, Rigshospitalet, Copenhagen University Hospital, Glostrup, Denmark
[13]Department of Rheumatology, Slagelse Hospital, Slagelse, Denmark
[14]Department of Rheumatology, Aalborg University Hospital, Aalborg, Denmark
[15]Department of Rheumatology, Vejle Hospital Lillebælt, Vejle, Denmark
[16]Department of Rheumatology, Frederiksberg Hospital, Copenhagen, Denmark
[17]Department of Rheumatology, Odense University Hospital, Odense C, Denmark
[18]Rheumatology Section, Department of Medicine M, Svendborg Hospital, Svendborg, Denmark
[19]Department of Rheumatology, Hospital Lillebælt, Fredericia, Kolding, Denmark
[20]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
[21]Zitelab Aps, Copenhagen, Denmark

Correction notice This article has been corrected since it published Online First. The author, Dorte Vendelbo Jensen, has been added.

Acknowledgements We are grateful to all Danish departments of rheumatology for reporting to the DANBIO registry.

Contributors Study conception and design: HN, SG, BG and MLH. Acquisition of data: HN, SG, BG, MLH, FM and NSK. Statistical analysis: HN, SG, BG and MLH. All authors contributed to the interpretation of the data. HN, SG, BG and MLH wrote the manuscript. All authors critically revised the manuscript. All authors revised and approved the final manuscript to be published.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests AGL: AbbVie, Eli Lilly Denmark A/S, Janssen-Cilag A/S, MSD, Novartis, Pfizer, UCB teaching or consultancy fees. OH: AbbVie, Pfizer, Novartis. MLH: AbbVie, Biogen, BMS, Celtrion, Eli Lilly Denmark A/S, Janssen Biologics BV, Lundbeck Fonden, MSD, Pfizer, Roche, Samsung Bioepis, Sandoz. Furthermore, chair of the steering committee of the Danish Rheumatology Quality Registry (DANBIO), which receives public funding from the hospital owners and funding from pharmaceutical companies. Co-chair EuroSpA, which generates real-world evidence of treatment of psoriatic arthritis and axial spondyloarthritis based on secondary data and is partly funded by Novartis. BG: BMS, Pfizer, Sandoz (research grants).

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Hafsah Nabi http://orcid.org/0000-0001-6331-7927
Stylianos Georgiadis http://orcid.org/0000-0003-3485-9457
Anne Gitte Loft http://orcid.org/0000-0001-6374-841X
Oliver Hendricks http://orcid.org/0000-0001-9473-5072
Marlene Andersen http://orcid.org/0000-0002-6803-0981
Stavros Chrysidis http://orcid.org/0000-0001-8583-6517
Ada Colic http://orcid.org/0000-0001-9873-4528
Kamilla Danebod http://orcid.org/0000-0001-6256-7430
Maren Høgberget Kalisz http://orcid.org/0000-0002-0434-6637
Salome Kristensen http://orcid.org/0000-0001-5812-5234
Niels Lomborg http://orcid.org/0000-0001-6871-9837
Heidi Lausten Munk http://orcid.org/0000-0002-2212-6283
Jens Kristian Pedersen http://orcid.org/0000-0003-2531-9537
Frank Mehnert http://orcid.org/0000-0001-7639-7356
Merete Lund Hetland http://orcid.org/0000-0003-4229-6818
Bente Glintborg http://orcid.org/0000-0002-8931-8482

REFERENCES

1 Schulze-Koops H, Skapenko A. Biosimilars in rheumatology: a review of the evidence and their place in the treatment algorithm. *Rheumatology* 2017;56:iv30–48.
2 Smolen JS, Goncalves J, Quinn M, *et al*. Era of biosimilars in rheumatology: reshaping the healthcare environment. *RMD Open* 2019;5:e000900.
3 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.
4 Cohen SB, Alonso-Ruiz A, Klimiuk PA, *et al*. Similar efficacy, safety and immunogenicity of adalimumab biosimilar BI 695501 and Humira reference product in patients with moderately to severely active rheumatoid arthritis: results from the phase III randomised VOLTAIRE-RA equivalence study. *Ann Rheum Dis* 2018;77:914–21.
5 Cohen SB, Czeloth N, Lee E, *et al*. Long-Term safety, efficacy, and immunogenicity of adalimumab biosimilar BI 695501 and adalimumab reference product in patients with

moderately-to-severely active rheumatoid arthritis: results from a phase 3B extension study (VOLTAIRE-RAext). *Expert Opin Biol Ther* 2019;19:1097–105.
6 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.
7 Cohen S, Pablos JL, Pavelka K, *et al*. An open-label extension study to demonstrate long-term safety and efficacy of ABP 501 in patients with rheumatoid arthritis. *Arthritis Res Ther* 2019;21:84.
8 Weinblatt ME, Baranauskaite A, Dokoupilova E, *et al*. Switching from reference adalimumab to SB5 (adalimumab Biosimilar) in patients with rheumatoid arthritis: Fifty-Two-Week phase III randomized study results. *Arthritis Rheumatol* 2018;70:832–40.
9 Weinblatt ME, Baranauskaite A, Niebrzydowski J, *et al*. Phase III randomized study of SB5, an adalimumab Biosimilar, versus reference adalimumab in patients with moderate-to-severe rheumatoid arthritis. *Arthritis Rheumatol* 2018;70:40–8.
10 Genovese MC, Glover J, Greenwald M, *et al*. FKB327, an adalimumab biosimilar, versus the reference product: results of a randomized, phase III, double-blind study, and its open-label extension. *Arthritis Res Ther* 2019;21:281.
11 Kay J. Biosimilars: New or Déj Vu? *Arthritis Rheumatol* 2016;68.
12 Rifkin RM, Peck SR, Azevedo V, Dörner T, Strohal R. Biosimilars: implications for clinical practice. *J Oncol Pract* 2017;13:13–18.
13 Reinisch W, Smolen J. Biosimilar safety factors in clinical practice. *Semin Arthritis Rheum* 2015;44:S9–15.
14 Concato J, Shah N, Randomized HRI, *et al*. Observational studies, and the hierarchy of research designs. *N Engl J Med* 2000;342:1887–92.
15 Hernán MA, Alonso A, Logan R, *et al*. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology* 2008;19:766–79.
16 Grøn KL, Glintborg B, Nørgaard M, *et al*. Comparative effectiveness of Certolizumab pegol, abatacept, and Biosimilar infliximab in patients with rheumatoid arthritis treated in routine care: observational data from the Danish DANBIO registry emulating a randomized trial. *Arthritis Rheumatol* 2019;71:1997–2004.
17 Implementation of Biosimilar adalimumab, Denmark. Available: https://medicinraadet.dk/media/svab0lxx/medicinraadets-vurdering-af-ibrugtagning-af-biosimilaer-adalimumab-version-10_adlegacy.pdf [Accessed 19 Jan 2021].
18 Jensen TB, Kim SC, Jimenez-Solem E, *et al*. Shift from adalimumab Originator to biosimilars in Denmark. *JAMA Intern Med* 2020;180:902–3.
19 New international record for switch to biosimilar - Amgros. Available: https://amgros.dk/en/knowledge-and-analyses/articles/new-international-record-for-switch-to-biosimilar/ [Accessed 5 Mar 2021].
20 Walker AM, Patrick AR, Lauer MS. A tool for assessing the feasibility of comparative effectiveness research. *Comp Eff Res* 2013;2013:3–11.
21 Craig P, Cooper C, Gunnell D, *et al*. Using natural experiments to evaluate population health interventions: new medical Research Council guidance. *J Epidemiol Community Health* 2012;66:1182–6.
22 Ibfelt EH, Jensen DV, Hetland ML. The Danish nationwide clinical register for patients with rheumatoid arthritis: DANBIO. *Clin Epidemiol* 2016;8:737–42.
23 Ibfelt EH, Sørensen J, Jensen DV, *et al*. Validity and completeness of rheumatoid arthritis diagnoses in the nationwide DANBIO clinical register and the Danish national patient registry. *Clin Epidemiol* 2017;9:627–32.
24 Schmidt M, Schmidt SAJ, Sandegaard JL, *et al*. The Danish national patient registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449.
25 Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–9.
26 Pocock SJ, Vandenbroucke JP. Strengthening the reporting of observational studies in epidemiology (StroBE) statement: guidelines for reporting observational studies.
27 White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30:377–99.
28 Lukas M, Malickova K, Kolar M, *et al*. Switching from Originator adalimumab to the Biosimilar SB5 in patients with inflammatory bowel disease: short-term experience from a single tertiary clinical centre. *J Crohns Colitis* 2020;14:915–9.
29 Ribaldone DG, Caviglia GP, Pellicano R, *et al*. Effectiveness and safety of adalimumab biosimilar ABP 501 in Crohn's disease: an observational study. *Rev Esp Enferm Dig* 2020;112:195–200.
30 Erskine D, Minshull -London J. Update on development of biosimilar versions of adalimumab with particular focus on excipients and injection site reactions. Available: https://www.ema.europ [Accessed 19 Jan 2021].
31 Hurley JC. How the Cluster-randomized Trial "Works". *Clin Infect Dis* 2020;70:341–6.
32 Gueyffier F, Cucherat M. The limitations of observation studies for decision making regarding drugs efficacy and safety. *Therapie* 2019;74:181–5.
33 Tweehuysen L, Huiskes VJB, van den Bemt BJF, *et al*. Open-Label, Non-Mandatory transitioning from Originator etanercept to Biosimilar SB4: six-month results from a controlled cohort study. *Arthritis Rheumatol* 2018;70:1408–18.
34 Tweehuysen L, van den Bemt BJF, van Ingen IL, *et al*. Subjective complaints as the main reason for Biosimilar discontinuation after open-label transition from reference infliximab to Biosimilar infliximab. *Arthritis Rheumatol* 2018;70:60–8.
35 Glintborg B, Lindström U, Aaltonen K, *et al*. Biological treatment in ankylosing spondylitis in the Nordic countries during 2010-2016: a collaboration between five biological registries. *Scand J Rheumatol* 2018;47:465–74.
36 Araújo FC, Gonçalves J, Fonseca JE. Pharmacoeconomics of biosimilars: what is there to gain from them? *Curr Rheumatol Rep* 2016;18.
37 Uhlig T, Goll GL. Reviewing the evidence for biosimilars: key insights, lessons learned and future horizons. *Rheumatology* 2017;56:iv49–62.
38 Glintborg B, Loft AG, Omerovic E, *et al*. To switch or not to switch: results of a nationwide guideline of mandatory switching from originator to biosimilar etanercept. one-year treatment outcomes in 2061 patients with inflammatory arthritis from the DANBIO registry. *Ann Rheum Dis* 2019;78:192–200.
39 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.
40 Glintborg B, Loft AG, Omerovic E, *et al*. Response to: 'Mandatory, cost-driven switching from originator etanercept to its biosimilar SB_4: possible fallout on non-medical switching' by Cantini and Benucci. *Ann Rheum Dis* 2020;79:e14.
41 Smits LJT, Grelack A, Derikx LAAP, *et al*. Long-Term Clinical Outcomes After Switching from Remicade® to Biosimilar CT-P13 in Inflammatory Bowel Disease. *Dig Dis Sci* 2017;62:3117–22.

EPIDEMIOLOGICAL SCIENCE

Effectiveness and treatment retention of TNF inhibitors when used as monotherapy versus comedication with csDMARDs in 15 332 patients with psoriatic arthritis. Data from the EuroSpA collaboration

Ulf Lindström ,[1] Daniela Di Giuseppe,[2] Bénédicte Delcoigne,[2] Bente Glintborg ,[3,4] Burkhard Möller ,[5] Adrian Ciurea ,[6] Manuel Pombo-Suarez,[7] Carlos Sanchez-Piedra,[8] Kari Eklund,[9,10] Heikki Relas,[9] Bjorn Gudbjornsson,[11,12] Thorvardur Jon Love,[12,13] Gareth T Jones ,[14] Catalin Codreanu,[15] Ruxandra Ionescu,[16] Lucie Nekvindova,[17,18] Jakub Závada,[19,20] Nuh Atas ,[21] Servet Yolbas,[22] Karen Minde Fagerli,[23] Brigitte Michelsen ,[23,24] Žiga Rotar,[25,26] Matija Tomšič,[25,26] Florenzo Iannone ,[27] Maria Jose Santos ,[28] Pedro Avila-Ribeiro,[29,30] Lykke Midtbøll Ørnbjerg,[31] Mikkel Østergaard,[31,32] Lennart TH Jacobsson,[1] Johan Askling ,[2] Michael J Nissen[33]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220097).

For numbered affiliations see end of article.

Correspondence to
Dr Ulf Lindström, Department of Rheumatology and Inflammation Research, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; ulf.lindstrom@gu.se

UL and DDG are joint first authors.

Received 5 February 2021
Accepted 24 May 2021
Published Online First 3 June 2021

To cite: Lindström U, Di Giuseppe D, Delcoigne B, *et al*. *Ann Rheum Dis* 2021;**80**:1410–1418.

ABSTRACT

Background Comedication with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) during treatment with tumour necrosis factor inhibitors (TNFi) is extensively used in psoriatic arthritis (PsA), although the additive benefit remains unclear. We aimed to compare treatment outcomes in patients with PsA treated with TNFi and csDMARD comedication versus TNFi monotherapy.

Methods Patients with PsA from 13 European countries who initiated a first TNFi in 2006–2017 were included. Country-specific comparisons of 1 year TNFi retention were performed by csDMARD comedication status, together with HRs for TNFi discontinuation (comedication vs monotherapy), adjusted for age, sex, calendar year, disease duration and Disease Activity Score with 28 joints (DAS28). Adjusted ORs of clinical remission (based on DAS28) at 12 months were calculated. Between-country heterogeneity was assessed using random-effect meta-analyses, combined results were presented when heterogeneity was not significant. Secondary analyses stratified according to TNFi subtype (adalimumab/infliximab/etanercept) and restricted to methotrexate as comedication were performed.

Results In total, 15 332 patients were included (62% comedication, 38% monotherapy). TNFi retention varied across countries, with significant heterogeneity precluding a combined estimate. Comedication was associated with better remission rates, pooled OR 1.25 (1.12–1.41). Methotrexate comedication was associated with improved remission for adalimumab (OR 1.45 (1.23–1.72)) and infliximab (OR 1.55 (1.21–1.98)) and improved retention for infliximab. No effect of comedication was demonstrated for etanercept.

Conclusion This large observational study suggests that, as used in clinical practice, csDMARD and TNFi comedication are associated with improved remission rates, and specifically, comedication with methotrexate increases remission rates for both adalimumab and infliximab.

Key messages

What is already known about this subject?

- Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are often used in combination with tumour necrosis factor (TNF)-inhibitors in psoriatic arthritis, although the added benefit of such comedication, over TNF-inhibitor monotherapy, has been disputed.

What does this study add?

- Treatment retention of TNF-inhibitors varied significantly across countries, as did the utilisation of a concomitant csDMARD, and overall, there was no additional improvement in TNF-inhibitor retention when used together with a csDMARD.
- Comedication with methotrexate in patients treated with adalimumab or infliximab was associated with a 50% increase in the probability of achieving DiseaseActivity Score with 28 joints (DAS28) remission at 1 year, compared with TNF-inhibitor monotherapy.
- Comedication with csDMARDs in patients treated with etanercept provided no additional advantage over TNF-inhibitor monotherapy, in terms of either retention or DAS28 remission rates.

How might this impact on clinical practice or future developments?

- Our findings support the prevailing clinical strategy of combining monoclonal TNF-inhibitors with methotrexate in psoriatic arthritis.

INTRODUCTION

Tumour necrosis factor inhibitors (TNFi) have become a cornerstone in the treatment of psoriatic

Table 1 Baseline characteristics (mean (SD) or percentages) of patients with PsA starting their first TNFi as monotherapy or in combination with a csDMARD, pooled across all countries

	TNFi and csDMARD co-medication		TNFi monotherapy	
		Proportion missing data		Proportion missing data
N (%)	9440 (62%)		5892 (38%)	
Age, years, mean (SD)	48.9 (12.1)	0%	49.0 (12.6)	0%
Sex (male), %	50%	0%	48%	0%
Disease duration, years mean (SD)	6.3 (7.1)	28%	6.2 (7.3)	32%
CRP, mg/L, mean (SD)	13.6 (21.3)	18%	9.1 (16.9)	25%
Tender joints 28, mean (SD)	6.2 (5.9)	21%	5.6 (6.1)	32%
Swollen joints 28, mean (SD)	3.9 (4.2)	21%	2.9 (4.0)	32%
VAS global health, mm, mean (SD)	59.2 (24.0)	21%	58.1 (25.6)	28%
VAS pain, mm, mean (SD)	57.4 (23.6)	30%	56.3 (25.7)	34%
DAPSA28, mean (SD)	28.8 (16.0)	38%	26.0 (16.9)	46%
DAS28-CRP, mean (SD)	4.2 (1.2)	29%	3.8 (1.3)	41%
Type of TNFi				
Adalimumab, %	32%	–	33%	–
Certolizumab pegol, %	6%	–	4%	–
Etanercept, %	30%	–	40%	–
Golimumab, %	11%	–	10%	–
Infliximab, %	20%	–	13%	–
Type of csDMARD used as co-medication				
Methotrexate, %	79%	–	–	–
Sulfasalazine, %	15%	–	–	–
Leflunomide, %	11%	–	–	–
Other*, %	6%	–	–	–

*See the list of all csDMARDs in Methods section.
CRP, C reactive protein; csDMARD, conventional synthetic disease modifying anti-rheumatic drugs; DAPSA28, disease activity index for psoriatic arthritis with 28 joints; DAS28-CRP, disease activity score with 28 joints and CRP; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitors; VAS, visual analogue scale.

arthritis (PsA). Despite this, no international consensus has been reached regarding the optimal use of TNFi in PsA. Thus, the current American College of Rheumatology guidelines recommend using TNFi as a first-line disease-modifying antirheumatic drug (DMARD), and, in patients previously failing a conventional synthetic conventional synthetic DMARD (csDMARD), to switch to rather than to add a TNFi.[1] In contrast, the European Alliance of Associations for Rheumatology (EULAR) recommendations suggest using csDMARDs (methotrexate in particular) as the first-line DMARD and to then step up the treatment by adding, rather than switching to, a biological DMARD, such as a TNFi.[2]

The discrepancy in international guidelines stems from the limited and conflicting data comparing the different treatment strategies. While the effect of TNFi has been compellingly demonstrated in all domains of PsA,[3] the effect of methotrexate is derived from expert opinion,[2] one large randomised clinical trial (RCT) (which failed to show an effect of methotrexate),[4] randomised trials not specifically designed to assess this effect[5 6] and a few smaller randomised trails.[7 8] The recent Study of Etanercept and Methotrexate in Subjects with Psoriatic Arthritis (SEAM)-trial, comparing etanercept and methotrexate monotherapy with combination therapy, demonstrated a superior response for etanercept compared with methotrexate, but additionally, a good response to methotrexate monotherapy.[9] Importantly, no additional effect of combination therapy over etanercept monotherapy was demonstrated.[9]

Available data so far suggest that csDMARD (especially methotrexate) and TNFi comedication therapy, compared with TNFi monotherapy, is not superior in terms of treatment response but may be beneficial for TNFi treatment retention.[10–14] Nevertheless, a recent study from a collaboration across European treatment registries (the European Spondyloarthritis Research collaboration Network: EuroSpA) indicated that 60% of patients with PsA starting a TNFi used a concomitant csDMARD, and that 81% had previously used a csDMARD, suggesting extensive use of comedication in routine care.[15] The 2019 EULAR recommendations for the management of PsA stipulate that more data are needed on this subject.[2]

The objective of this observational study of patients with PsA in routine care was, therefore, to compare the 1-year TNFi treatment retention and treatment response on joint manifestations, in patients starting a first TNFi as monotherapy compared with those starting a TNFi as combination therapy, that is, together with a csDMARD.

METHODS

This is an observational study based on prospectively collected data from 13 rheumatology registers in Europe, aggregated through the EuroSpA collaboration (as previously described[15]).

Data sources

Patients with PsA, aged 18 years or older, starting a first TNFi (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) in 2006–2017 were identified from the following countries (registers): Czech Republic (ATTRA), Denmark (DANBIO), Finland (ROB-FIN), Iceland (ICEBIO), Italy (GISEA), Norway (NOR-DMARD), Portugal (Reuma.pt), Romania (RRBR), Slovenia (biorx.si), Spain (BIOBADASER), Sweden (ARTIS), Switzerland (SCQM) and Turkey (TURKBIO).

Time-point definitions and treatment groups

All participating registers recorded start dates (and stop dates in case of withdrawal) for the TNFi. The start date of the patients' first TNFi was set as the baseline date, and the baseline visit was defined as the visit closest to the registered start date, within −100 to +30 days, giving priority to dates before the start date. The 3-month, 6-month and 12-month follow-up visits during treatment were defined as the date of visit closest to these time points, within the ranges: day 60–150, day 151–270 and day 271–545, respectively, counting from the baseline date.

Registration of csDMARD use varied across the registers, with some recording start and stop dates, while others record treatment status (use/no use) at registered visits. Thus, comedication use was either based on the start and stop dates (where available) for the csDMARD or on data on treatment status at registered visits.

The following two treatment exposure groups were defined: (1) The TNFi monotherapy group (=monotherapy group) including all patients starting a first TNFi without concurrent use of a csDMARD in a period from 100 days before to 30 days after baseline and (2) The TNFi and csDMARD comedication group (=comedication group) including all patients either starting a first TNFi together with a csDMARD (within 30 days) or starting a TNFi added to an already ongoing (and continued) csDMARD treatment. Changes in csDMARD treatment (withdrawal or

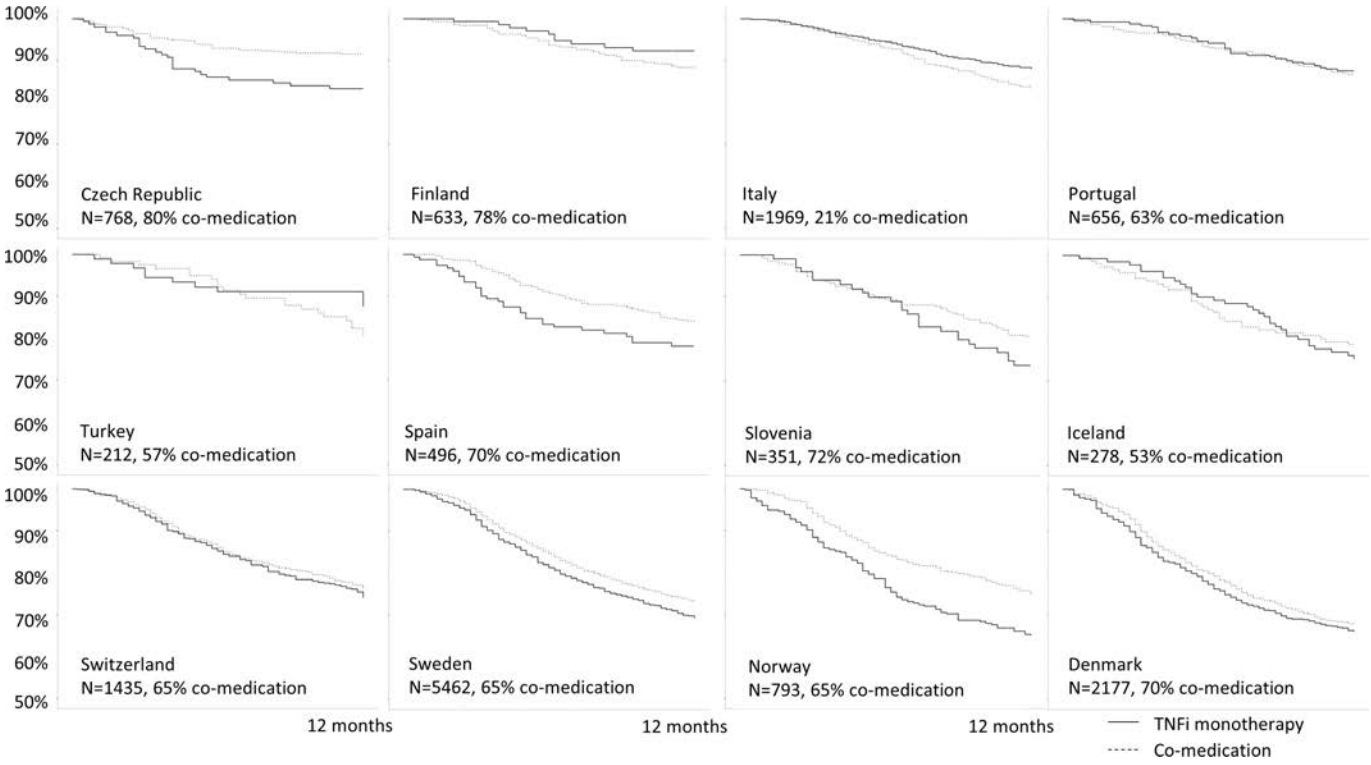


Figure 1 Country-specific 1 year treatment retention of co-medication and TNFi monotherapy (Kaplan-Meier retention curves), ordered by overall TNFi retention of the countries, from highest to lowest. Romania is not included in the figure due to <5 patients in the monotherapy group. TNFi, tumour necrosis factor inhibitors.

switch to other csDMARD) during follow-up beyond 30 days from the baseline visit were not considered.

In the main analyses, the following csDMARDs were included: methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, chloroquine, cyclosporine, azathioprine, mycophenolate and cyclophosphamide.

Patients were followed up from the baseline date until first of: TNFi stop date, last visit date +12 months, end of patient's participation in the register or end of the study period (31 December 2017).

Treatment retention

The 1-year treatment retention of the TNFi in the two treatment groups was compared through crude survival curves (Kaplan-Meier curves), and as HRs for TNFi discontinuation, with monotherapy as the reference.

Treatment response

Clinical remission at 12 months of treatment was defined following a hierarchical approach (online supplemental figure S1): for patients remaining on TNFi treatment beyond 12 months, clinical remission was defined as 28-joint Disease Activity Score with 28 joints and CRP (DAS28-CRP) <2.6 at the 12- month visit.[16] For patients with follow-up and treatment longer than 12 months, but with DAS28 missing at the 12-month visit, a DAS28 recorded at 6 months and up to 12 months was carried forward. Patients discontinuing the TNFi before 12 months due to adverse events or lack of effect were considered not having achieved remission. Patients discontinuing the TNFi due to remission and not starting another TNFi before 12 months (27 patients) were considered as remaining in remission. Patients discontinuing the TNFi before 12 months for other reasons (eg, pregnancy) were considered as missing data. The reason for TNFi discontinuation was missing in only 11% of the patients with monotherapy and 3% with comedication.

Statistical analyses

Baseline characteristics of the patients are presented country specific and pooled for all countries, as means and SD (continuous variables) or percentages (categorical variables).

Significant heterogeneity between countries was anticipated for both TNFi retention and treatment response. Therefore, all analyses were first performed individually per country, and only after disproving heterogeneity, combined results were presented (see below).

Country-specific HR of TNFi discontinuation was estimated using Cox regression adjusted for age, sex, calendar year, DAS28-CRP and disease duration at baseline.

Country-specific response rates of the two treatment groups were compared, based on the proportions and ORs of achieving clinical remission at 12 months and visualised through the average across individual patients' delta-(Δ)-DAS28-CRP (baseline DAS28-CRP minus 12 month's DAS28-CRP). ORs of achieving remission at 12 months (yes/no) were estimated using logistic regression adjusted for the same variables as mentioned above.

Overall results from both the Cox regression and the logistic regression analyses, per country, were combined using a random-effect meta-analysis. Statistical heterogeneity among countries was evaluated with the Cochran Q-test and the I^2 statistic in order to assess the proportion of total variation that was due to between-country variation, based on the included cases with nonmissing data on the respective outcome.[17]

All data are reported as observed. No imputation of missing data was performed. In the regression models, baseline disease duration and DAS28 were categorised into quartiles to enable

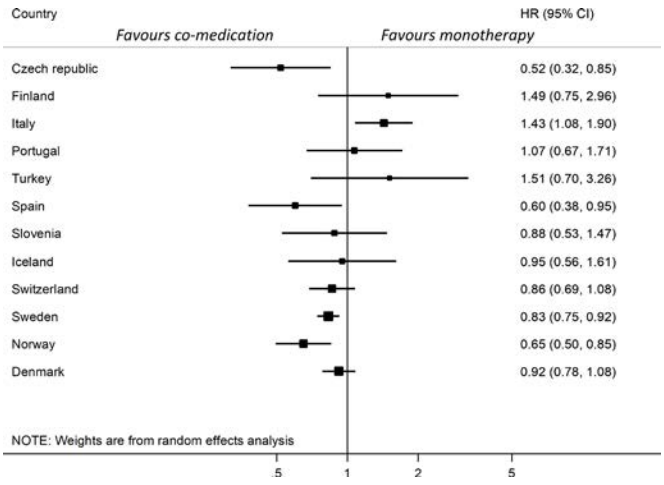


Figure 2 Forest plot of country-specific hazard ratios for TNFi discontinuation at 12 months comparing TNFi and csDMARD co-medication with TNFi monotherapy, ordered by overall TNFi retention rate per country. Adjusted for baseline age, sex, calendar year, DAS28 and disease duration. Combined results are not presented due to significant heterogeneity. Data from Romania are not presented due to <5 patients with monotherapy. csDMARDs,conventional synthetic disease-modifying anti-rheumatic drugs; DAS28, Disease Activity Score with 28 joints; TNFi, tumour necrosis factor inhibitors.

the use of a fifth category for missing data. The effectiveness analyses were modelled only on patients with remission outcome data, and DAS28 at 6 months was carried forward if missing at 12 months.

Retention and effectiveness analyses were performed using R, V.3.6.3 (R Core Team (2020)). Meta-analyses were performed using Stata, V.14.2 (StataCorp, College Station, Texas, USA). Throughout all analyses, the level of statistical significance was set to 0.05. The proportional hazards assumption (for retention analyses) was assessed using the cox.zph function of the R survival package.

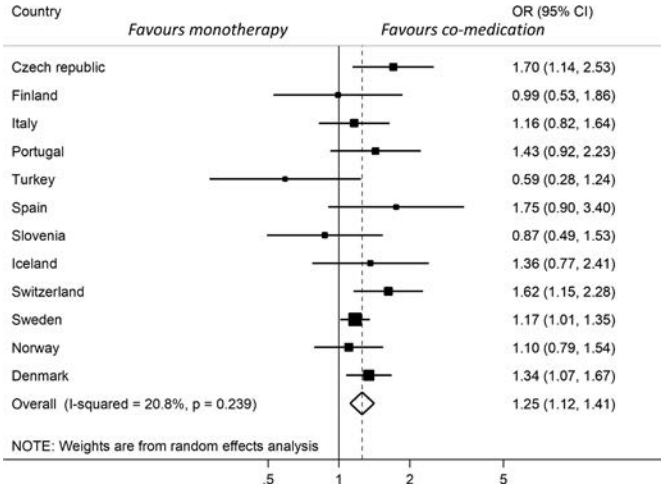


Figure 3 Forest-plot of country-specific ORs and overall OR for clinical remission at 12 months in TNFi and csDMARD co-medication compared with TNFi monotherapy. Adjusted for baseline age, sex, calendar year, DAS28 and disease duration. Data from Romania are not presented separately due to <5 patients with monotherapy. csDMARDs,conventional synthetic disease-modifying anti-rheumatic drugs; DAS28, Disease Activity Score with 28 joints; TNFi, tumour necrosis factor inhibitors.

Secondary analyses

All initial analyses were performed combining data for the different TNFi. Biosimilars were not distinguished from originators, and switches between originators and corresponding biosimilars were disregarded.

Due to the potential differential effect of csDMARD comedication according to the type of TNFi and comedication, secondary analyses were performed separately for the subgroup of patients treated with the most common TNFi (infliximab, adalimumab and etanercept: constituting 82% of the TNFi in the comedication group and 86% in the monotherapy group) and exploring the most common csDMARD, that is, methotrexate. In these subset analyses, country-specific comparisons were only performed if at least 30 patients were included in each of the treatment groups.

Patient and public involvement

Patients were not involved in the study.

RESULTS

In total, 15 332 patients starting a TNFi were included, of whom 9440 (62%) were included in the comedication group (table 1) and 5892 (38%) in the TNFi monotherapy group.

Methotrexate was the most frequently used csDMARD (79%). There was a large variation in the proportion of monotherapy versus comedication across registers (monotherapy 1%–79%, figure 1 and online supplemental table S2). Overall, baseline characteristics were similar between the two treatment groups, with a slightly higher DAS28-CRP in the comedication group compared with the monotherapy group (4.2 vs 3.8, p value <0.001), a higher proportion of patients treated with infliximab in the comedication group and a higher proportion with etanercept in the monotherapy group. The mean number of swollen and tender joints was also higher in the comedication group. Baseline characteristics per country are presented in online supplemental table S2 and the proportions of missing data in online supplemental table S3. Data from one register (Romania) were excluded from the stratified analyses due to a large imbalance between the treatment groups (<5 patients included in the monotherapy group).

Treatment retention

The overall treatment retention of the TNFi differed between the countries, and the heterogeneity was statistically significant (I^2=62.7%; p=0.002). It was, therefore, determined inappropriate to proceed with presentation of the combined result in a meta-analysis. The country-specific crude retention curves (figure 1) showed not only modest differences between the two treatment groups but also different directions of the effect of comedication versus TNFi monotherapy across countries. The retention curves of the individual countries by csDMARD use, demonstrated in figure 1, are ordered by the overall retention rates (from highest to lowest) of the TNFi in the registers. The overall TNFi retention regardless of comedication is shown in online supplemental figure S2.

The country-specific HR for discontinuation, adjusted for age, sex, calendar year, disease duration and DAS28, also showed different directions for the association between drug retention and use of comedication (figure 2). The HRs in eight of the countries were below 1 (range 0.52–0.95), indicating better retention for comedication, and above 1 in four countries (range 1.07–1.51) favouring monotherapy, but only in five of all 12 countries were these findings statistically significant, figure 2. The assumption of proportional hazards was not rejected for all countries but Spain. Due to the clear direction of the results in Spain, this was not analysed further.

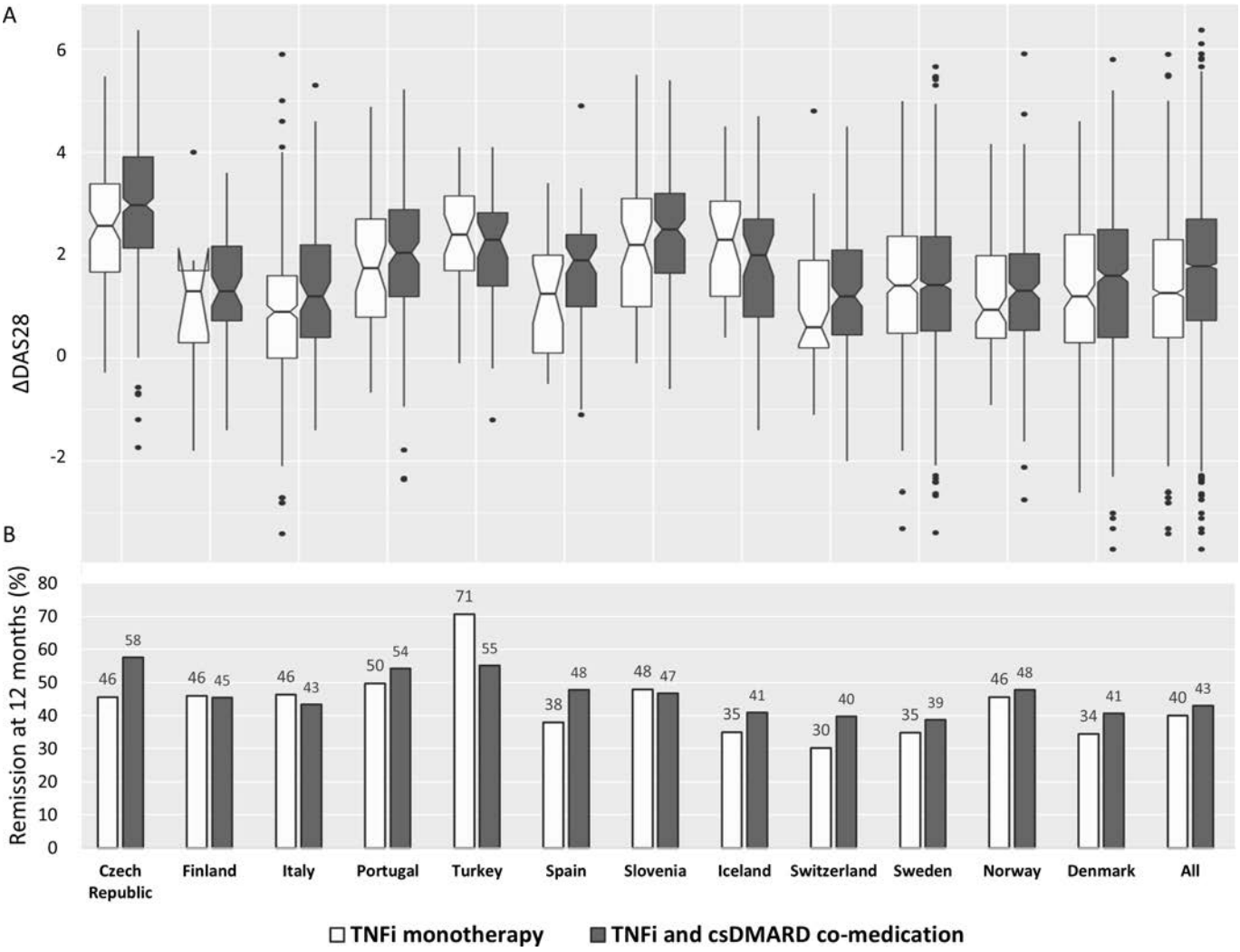


Figure 4 DAS28-CRP response at 12 months per country.(A) Delta DAS28-CRP between baseline and 12 months. (B) Proportions achieving remission at 12 months. Data from Romania are not presented due to <5 patients with monotherapy. csDMARDs,conventional synthetic disease-modifying ant-irheumatic drugs; DAS28, Disease Activity Score with 28 joints; TNFi, tumour necrosis factor inhibitors.

Treatment response

In contrast to the retention rates, the variation in response rates across the included countries was less pronounced, and there was no significant heterogeneity (I^2=20.8%; p=0.239). The overall OR for achieving clinical remission at 12 months in the comedication group versus the monotherapy group was 1.25 (1.12–1.41) favouring comedication (figure 3). Excluding the two countries considered to be outliers in terms of the proportion of patients on comedication treatment (21% and 99%) resulted in a very similar pooled OR of 1.27 (1.11–1.44) for remission. The ΔDAS28-CRP and the crude proportions achieving remission across the different registers (figure 4A,B) also suggested a tendency towards better outcomes in the co-medication groups. In total, 72% of the patients had complete outcome data and were included in the response analyses. Regarding patients in the csDMARD group who remained on the TNFi at 6 months, 82% also remained on csDMARD treatment.

Secondary analyses

The results of the secondary analyses, assessing the effect of methotrexate comedication separately for infliximab, adalimumab and etanercept, are presented in table 2.

Only three countries provided enough patients for all different strata of the secondary analyses. The number of patients included in the secondary analyses is presented in online supplemental table S4. In general, the differences in crude retention rates and the proportion reaching clinical remission were modest across the different TNFi, particularly between etanercept and adalimumab. The retention rate of etanercept was in line with that of the adalimumab comedication groups and somewhat higher than the infliximab groups (table 2). In four out of five contributing countries, the HR for infliximab discontinuation was in favour of methotrexate comedication, but this was only statistically significant in two of the countries. For adalimumab, the HR of TNFi discontinuation was in favour of methotrexate comedication in 7 out of 10 contributing countries (with statistically significant values below 1 in two countries and above 1 in one country). For etanercept, the HR of discontinuation was in favour of methotrexate comedication in five countries and in favour of monotherapy in four contributing countries (all results were nonsignificant).

The combined OR for remission indicated better outcomes for methotrexate comedication compared with monotherapy for infliximab (1.55 (1.21–1.98)) and adalimumab (1.45 (1.23–1.72)), whereas no such association was observed for etanercept (1.12 (0.95–1.31)).

Table 2 Crude TNFi retention and adjusted HR for TNFi discontinuation (upper part of table), and crude proportion achieving remission and adjusted OR for clinical remission (lower part of table) for infliximab, adalimumab and etanercept, in co-medication with methotrexate compared with monotherapy

		Infliximab	Adalimumab	Etanercept
One-year TNFi retention (%) and adjusted* HR for TNFi discontinuation (ref=monotherapy)				
Czech republic	co-med/mono	NA	92%/79%	89%/89%
	HR (95% CI)	NA	**0.36 (0.17 to 0.77)**	1.06 (0.31 to 3.63)
Finland	co-med/mono	NA	87%/90%	95%/96%
	HR (95% CI)	NA	1.18 (0.41 to 3.35)	2.08 (0.31 to 13.94)
Italy	co-med/mono	80%/87%	82%/88%	85%/89%
	HR (95% CI)	1.45 (0.63 to 3.35)	1.63 (0.98 to 2.72)	1.45 (0.84 to 2.51)
Portugal	co-med/mono	NA	89%/97%	89%/84%
	HR (95% CI)	NA	**7.39 (1.46 to 37.54)**	0.60 (0.28 to 1.30)
Spain	co-med/mono	NA	82%/82%	77%/78%
	HR (95% CI)	NA	0.70 (0.26 to 1.90)	0.76 (0.30 to 1.90)
Slovenia	co-med/mono	NA	80%/67%	NA
	HR (95% CI)	NA	0.90 (0.41 to 1.96)	NA
Iceland	co-med/mono	81%/78%	NA	NA
	HR (95% CI)	0.81 (0.39 to 1.70)	NA	NA
Switzerland	co-med/mono	77%/73%	79%/72%	80%/78%
	HR (95% CI)	0.78 (0.39 to 1.58)	0.67 (0.45 to 1.00)	0.81 (0.49 to 1.35)
Sweden	co-med/mono	71%/63%	78%/66%	76%/74%
	HR (95% CI)	**0.65 (0.50 to 0.85)**	**0.58 (0.47 to 0.72)**	0.94 (0.77 to 1.14)
Norway	co-med/mono	NA	83%/68%	81%/70%
	HR (95% CI)	NA	0.59 (0.24 to 1.48)	0.59 (0.35 to 1.01)
Denmark	co-med/mono	64%/45%	71%/70%	70%/72%
	HR (95% CI)	**0.56 (0.41 to 0.78)**	0.93 (0.70 to 1.24)	1.12 (0.77 to 1.62)
Crude proportion (%) reaching remission at 12 months and adjusted* OR for clinical remission (ref=monotherapy)				
Pooled	co-med/mono	38%/32%	47%/38%	44%/42%
	OR (95% CI)	**1.55 (1.21 to 1.98)**	**1.45 (1.23 to 1.72)**	1.12 (0.95 to 1.31)
Czech republic	co-med/mono	NA	57%/38%	68%/57%
	OR (95% CI)	NA	**2.25 (1.23 to 4.20)**	1.69 (0.66 to 4.33)
Finland	co-med/mono	NA	NA	NA
	OR (95% CI)	NA	NA	NA
Italy	co-med/mono	29%/42%	43%/45%	46%/47%
	OR (95% CI)	0.59 (0.12 to 2.58)	1.07 (0.55 to 2.07)	1.09 (0.59 to 2.02)
Portugal	co-med/mono	NA	54%/49%	51%/54%
	OR (95% CI)	NA	1.26 (0.49 to 3.27)	1.40 (0.64 to 3.15)
Spain	co-med/mono	NA	NA	NA
	OR (95% CI)	NA	*NA*	NA
Slovenia	co-med/mono	NA	42%/47%	NA
	OR (95% CI)	NA	0.69 (0.28 to 1.68)	NA
Iceland	co-med/mono	NA*	NA	NA
	OR (95% CI)	NA*	NA	NA
Switzerland	co-med/mono	NA	40%/33%	37%/21%
	OR (95% CI)	NA	1.68 (0.94 to 3.06)	***2.94 (1.28 to 7.18)***
Sweden	co-med/mono	37%/27%	43%/33%	41%/38%
	OR (95% CI)	**1.73 (1.17 to 2.60)**	**1.59 (1.2 to 2.11)**	1.03 (0.82 to 1.31)
Norway	co-med/mono	NA	54%/47%	49%/50%
	OR (95% CI)	NA	1.58 (0.54 to 4.66)	0.95 (0.52 to 1.74)
Denmark	co-med/mono	34%/21%	45%/37%	42%/37%
	OR (95% CI)	**2.01 (1.13 to 3.72)**	1.42 (0.99 to 2.03)	1.15 (0.72 to 1.85)

HR and OR are adjusted for age, sex, calendar year, disease duration and DAS28-CRP.
co-med/mono indicates the crude 1 year TNFi retention rate and the proportion in the co-medication/monotherapy groups reaching remission, respectively.
*NA=not available due to <30 patients in at least one of the exposure groups. Data from Romania and Turkey are not included in the table because they provided no strata in the analysis with ≥30 patients in both groups. Adjusted for baseline age, sex, calendar year, DAS28-CRP and disease duration.
CRP, C reactive protein; DAS28, Disease Activity Score with 28 joints; TNFi, tumour necrosis factor inhibitors.

The distribution of DAS28 and the number of tender and swollen joints at baseline in the secondary analyses are presented in online supplemental figure S3. The comedication treatment groups were associated with higher baseline values of both DAS28 and number of swollen joints, indicating more active peripheral joint disease.

DISCUSSION

In this study of 15 332 patients with PsA initiating a first ever TNFi, based on data from 13 European countries, we found that csDMARD comedication was associated with a 25% improved rate of clinical remission at 12 months, compared with TNFi

monotherapy. Regarding TNFi treatment retention, the results varied across the countries and no combined estimate could be assessed due to the significant heterogeneity. In the secondary analyses, significantly improved remission rates were observed for adalimumab and infliximab when used together with methotrexate, and a trend towards better treatment retention for infliximab, while no advantage was found for combining etanercept with methotrexate.

The initial RCTs for etanercept,[18] infliximab[19] and adalimumab[20] did not indicate a difference in response between patients on monotherapy versus comedication with methotrexate, although these trials were generally restricted to patients with inadequate response to csDMARD. Similarly, the recent SEAM-trial[9] and previous observational studies have in general not indicated any additional treatment response for methotrexate when used in combination with a TNFi,[10] although several studies have demonstrated improved TNFi retention.[10–13 21] Based on these previous studies, our finding of an increased proportion achieving clinical remission in the csDMARD comedication group was unexpected.

Another recent register-based study (including data from three of the same registers, as the present study: Italy, Czech Republic and Switzerland) found no effect of comedication on treatment response.[22] However, in that study, all TNFi were analysed together. By contrast, the results of our stratified secondary analysis suggest that clear differences between the TNFi can explain some of this discrepancy and that combining the drug-specific effects may have diluted the overall effect observed in that study. In line with previous studies, we found a trend for better TNFi treatment retention for infliximab, when used together with methotrexate, but not for etanercept, which corroborates the results from the SEAM trial.[9] Further and similar to the SEAM trial, we found no additive effect on treatment response of methotrexate when added to etanercept.[9] Our findings of a 55% and 45% higher odds for reaching remission at 12 months in the methotrexate comedication groups of infliximab and adalimumab, respectively, are novel findings. In particular, for adalimumab, the validity of these results is supported by the fact that all except one of the countries, included in that analysis, presented ORs in the same direction.

This study has some limitations. First, in contrast to the relatively uniform results for the response rates, the pronounced intercountry differences in TNFi retention suggests that factors other than biological/pharmaceutical may have an influence on observed retention rates. Since the understanding of how such factors (eg, availability of drugs, prescription regulations and insurance policies) may influence the retention rates is incomplete, it was deemed beyond the scope of this paper to explore this further. However, these findings suggest that treatment retention should be analysed in a way that accounts for such factors, and that pooling of retention data across countries should be performed with caution. Furthermore, use of csDMARD comedication in TNFi-treated patients varied from 21% to 99% across the registers, suggesting large differences in treatment strategies in the participating countries. However, we do not believe that this biases the results, since excluding the outliers barley changed the pooled response outcome, and since there were no clear correlations between the proportions treated with comedication, and the direction and magnitude of remission and retention rates.

Second, use of 28-joint counts to define remission in PsA is inferior to the recommended 66/68-joint counts. However, this should not introduce a bias across the exposure groups, particularly not with regards to differentiation between axial and peripheral disease.

Third, misclassification may be an issue, and since PsA classification criteria are not uniformly registered across the registers, case ascertainment was based on the clinical diagnosis entered by the treating rheumatologist. When aggregating data from a large number of different registers, further difficulties arise regarding the operational definitions of exposures and outcomes and in assessment of nonrandom missing data. Fourth, of the 13 countries initially included, only three contributed enough patients to be included in all analyses (including secondary analyses). The large differences in the number of patients from each register will also inevitably lead to an unequal impact on the combined results.

Fifth, confounding by indication is likely to affect the results, since both the choice of TNFi and the decision to use csDMARD comedication may be influenced by factors such as axial versus peripheral disease, the extent of cutaneous psoriasis and other comorbidities. In this study, we could not precisely identify axial disease or other concomitant comorbidities. In the secondary analyses, the baseline distributions of swollen joint count and DAS28 (online supplemental figure 3) suggested that patients with methotrexate comedication had a higher peripheral joint disease activity, despite having higher OR of reaching clinical remission, thus supporting an effect of comedication.

Finally, changes in csDMARD treatment over the 1-year follow-up period were not taken into account, since it was not within the aims of the present study to assess csDMARD retention and since csDMARD data (eg, doses and start/stop dates) are poorly captured in the majority of the registers.

Conversely, our study has several strengths. First, it includes a large number of patients with PsA with prospectively collected data. Second, the possibility of comparing retention and response rates across several different registers and to assess heterogeneity, adds considerable robustness to the results and their interpretation. Third, the large number of patients enabled stratification of the analysis according to the type of TNFi and methotrexate comedication.

In conclusion, we found improved clinical response rates when combining TNFi with a csDMARD. More specifically, the rate of clinical remission for infliximab and adalimumab increased when combined with methotrexate, and the retention of infliximab was improved. For etanercept, the remission and retention rates did not differ between comedication and monotherapy—and were in line with the rates observed for adalimumab comedication. Our findings support the prevailing strategy, in a situation of incomplete response, to continue methotrexate therapy when commencing treatment with infliximab or adalimumab, while for etanercept methotrexate may be discontinued.

Author affiliations
[1]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[2]Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden
[3]DANBIO and Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre of Head and Orthopedics, Rigshospitalet, Copenhagen, Denmark
[4]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[5]Department for Rheumatology and Immunology, Inselspital University Hospital Bern, Bern, Switzerland
[6]Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[7]Rheumatology Service, Hospital Clinico Universitario, Santiago de Compostela, Spain
[8]Research Unit, Spanish Society of Rheumatology, Madrid, Spain
[9]Inflammation Center, Department of Rheumatology, Helsinki University Hospital, Helsinki, Finland

[10]Orton Orthopaedic Hospital, Helsinki, Finland
[11]Centre for Rheumatology Research, University Hospital, Reykjavik, Iceland
[12]Faculty of Medicine, University of Iceland, Reykjavik, Iceland
[13]Department for Science and Research, Landspitali University Hospital, Reykjavik, Iceland
[14]Epidemiology Group, Aberdeen Centre for Arthritis and Musculoskeletal Health, University of Aberdeen, Aberdeen, UK
[15]Romanian Registry of Rheumatic Diseases, University of Medicine and Pharmacy, Bucharest, Romania
[16]Romanian Registry of Rheumatic Diseases, University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania
[17]First Faculty of Medicine, Charles University, Prague, Czech Republic
[18]Institute of Biostatistics and Analyses, Ltd, Brno, Czech Republic
[19]Department of Rheumatology, First Faculty of Medicine, Charles University, Prague, Czech Republic
[20]Institute of Rheumatology, Prague, Czech Republic
[21]Division of Rheumatology, Department of Internal Medicine, University Hospital and Faculty of Medicine, Gazi University, Ankara, Turkey
[22]Division of Rheumatology, Department of Internal Medicine, University Hospital and Faculty of Medicine, Inonu University, Malatya, Turkey
[23]Department of Rheumatology and Research, Diakonhjemmet Hospital, Oslo, Norway
[24]Division of Rheumatology, Department of Medicine, Sorlandet Hospital, Kristiansand, Norway
[25]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia
[26]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[27]Rheumatology Unit—DETO, University of Bari, Bari, Italy
[28]Reuma.pt registry and Department of Rheumatology, Hospital Garcia de Orta, Almada, Portugal
[29]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal
[30]Rheumatology Department, Hospital de Santa Maria, Lisboa, Portugal
[31]Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre for Head and Orthopaedics, Rigshospitalet Glostrup, Glostrup, Denmark
[32]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[33]Department of Rheumatology, Geneva University Hospital, Geneva, Switzerland

Twitter Gareth T Jones @hteraG_senoJ

Contributors All coauthors have contributed significantly in accordance with contributorship guidelines.

Funding This work was supported by Novartis. Novartis had no influence on the data collection, statistical analyses, manuscript preparation or decision to submit. The work was also supported by NordForsk.

Competing interests BeG reports grants from BMS, grants from Pfizer, grants from AbbVie, outside the submitted work. AC reports consultancy and speaker fees from Abbvie, Eli Lilly, Merck Sharp & Dohme, Novartis and Pfizer. MP-S reports speaker and research fees from Gilead, Janssen, MSD and Sanofi. KE reports consulting fees from Lilly, Biogene, Sobi, Pfizer and Gilead. HR reports personal fees from AbbVie, personal fees from Roche, personal fees from Pfizer, outside the submitted work. BjG reports other from Novartis, other from Amgen, outside the submitted work. GTJ reports grants from AbbVie, grants from Pfizer, grants from UCB, grants from Celgene / Amgen, grants from GSK, outside the submitted work. CC reports speaker fees and grants from AbbVie, Amgen, Egis, Novartis, Pfizer and UCB. RI reports speaker fee from Abbvie, Amgen, Novartis, Pfizer, Lilly and UCB. JZ reports speaker and consulting fees from Elli-Lilly, Abbvie, Novartis and UCB. SY reports speaker fees from Abbvie, MSD, Novartis, UCB, Sanofi and Pfizer. BM reports grants and personal fees from Novartis, outside the submitted work. ZR reports speaker fees, consultancy fees and support to biorx.si registry by, AbbVie, Amgen, Biogen, Eli Lilly, Janssen, Medias, Medis, MSD, Novartis, OPH Oktal Pharma, Sandoz and Pfizer. MTreports speaker fees, consultancy fees and support to biorx.si registry by, AbbVie, Amgen, Biogen, Eli Lilly, Janssen, Medias, Medis, MSD, Novartis, OPH Oktal Pharma, Sandoz and Pfizer. FI reports consultancy fees and/or speaker honoraria from Pfizer, AbbVie, MSD, BMS, Lilly, Novartis, Sanofi, Celgene and UCB, outside this work. MJS reports personal fees from Abbvie, Novartis and Pfizer, outside the submitted work. PA-R reports research grant (paid to academic research institute) from Novartis. LMØ reports grants from Novartis, during the conduct of the study. MØ reports grants, personal fees and non-financial support from AbbVie, grants, personal fees and non-financial support from BMS, personal fees from Boehringer-Ingelheim, personal fees from Eli Lilly, personal fees and non-financial support from Janssen, grants, personal fees and non-financial support from Merck, personal fees and non-financial support from Pfizer, personal fees and non-financial support from Roche, grants, personal fees and non-financial support from UCB, grants and personal fees from Celgene, personal fees from Sanofi, personal fees from Regeneron, grants, personal fees and non-financial support from Novartis, personal fees from Gilead, outside the submitted work. LJ reports lecture and consulting fees from Pfizer, Abbvie, Novartis, Eli-Lily and Janssen. JA reports grants from Abbvie, Astra-Zeneca, BMS, Eli Lilly, MSD, Pfizer, Roche, Samsung Bioepis, Sanofi, and UCB, outside the submitted work. MN reports research and consulting fees from Abbvie, Celgene, Eli-Lilly, Janssen, Novartis and Pfizer.

Patient consent for publication Not required.

Ethics approval The study was approved by the respective national data protection agencies and research ethical committees according to legal regulatory requirements in the participating countries (online supplemental table S1).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

ORCID iDs
Ulf Lindström http://orcid.org/0000-0002-2250-9348
Bente Glintborg http://orcid.org/0000-0002-8931-8482
Burkhard Möller http://orcid.org/0000-0001-8769-6167
Adrian Ciurea http://orcid.org/0000-0002-7870-7132
Gareth T Jones http://orcid.org/0000-0003-0016-7591
Nuh Atas http://orcid.org/0000-0001-5880-4974
Brigitte Michelsen http://orcid.org/0000-0003-0103-2840
Florenzo Iannone http://orcid.org/0000-0003-0474-5344
Maria Jose Santos http://orcid.org/0000-0002-7946-1365
Johan Askling http://orcid.org/0000-0003-0433-0616

REFERENCES

1 Singh JA, Guyatt G, Ogdie A, *et al*. Special article: 2018 American College of Rheumatology/National psoriasis Foundation guideline for the treatment of psoriatic arthritis. *Arthritis Rheumatol* 2019;71:5–32.
2 Gossec L, Baraliakos X, Kerschbaumer A, *et al*. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* 2020;79:700.1–12.
3 Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. *N Engl J Med* 2017;376:957–70.
4 Kingsley GH, Kowalczyk A, Taylor H, *et al*. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology* 2012;51:1368–77.
5 Baranauskaite A, Raffayová H, Kungurov NV, *et al*. Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the respond study. *Ann Rheum Dis* 2012;71:541–8.
6 Coates LC, Moverley AR, McParland L, *et al*. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet* 2015;386:2489–98.
7 Willkens RF, Williams HJ, Ward JR, *et al*. Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. *Arthritis Rheum* 1984;27:376–81.
8 Scarpa R, Peluso R, Atteno M, *et al*. The effectiveness of a traditional therapeutical approach in early psoriatic arthritis: results of a pilot randomised 6-month trial with methotrexate. *Clin Rheumatol* 2008;27:823–6.
9 Mease PJ, Gladman DD, Collier DH, *et al*. Etanercept and methotrexate as monotherapy or in combination for psoriatic arthritis: primary results from a randomized, controlled phase III trial. *Arthritis Rheumatol* 2019;71:1112–24.
10 Behrens F, Cañete JD, Olivieri I, *et al*. Tumour necrosis factor inhibitor monotherapy vs combination with MTX in the treatment of PsA: a systematic review of the literature. *Rheumatology* 2015;54:915–26.
11 George MD, Baker JF, Ogdie A. Comparative persistence of methotrexate and tumor necrosis factor inhibitors in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. *J Rheumatol* 2020;47:826–34.
12 Kristensen LE, Gülfe A, Saxne T, *et al*. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish arthritis treatment group register. *Ann Rheum Dis* 2008;67:364–9.

13 Fagerli KM, Lie E, van der Heijde D, *et al*. The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: results from 440 patients included in the NOR-DMARD study. *Ann Rheum Dis* 2014;73:132–7.
14 Maneiro JR, Souto A, Salgado E, *et al*. Predictors of response to TNF antagonists in patients with ankylosing spondylitis and psoriatic arthritis: systematic review and meta-analysis. *RMD Open* 2015;1:e000017.
15 Brahe CH, Ørnbjerg LM, Jacobsson L, *et al*. Retention and response rates in 14 261 PsA patients starting TNF inhibitor treatment-results from 12 countries in EuroSpA. *Rheumatology* 2020;59:1640–50.
16 Michelsen B, Sexton J, Smolen JS, *et al*. Can disease activity in patients with psoriatic arthritis be adequately assessed by a modified disease activity index for psoriatic arthritis (DAPSA) based on 28 joints? *Ann Rheum Dis* 2018;77:1736–41.
17 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
18 Mease PJ, Kivitz AJ, Burch FX, *et al*. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004;50:2264–72.
19 Antoni CE, Kavanaugh A, Kirkham B, *et al*. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). *Arthritis Rheum* 2005;52:1227–36.
20 Mease PJ, Gladman DD, Ritchlin CT, *et al*. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005;52:3279–89.
21 Glintborg B, Østergaard M, Dreyer L, *et al*. Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor α therapy: results from the nationwide Danish DANBIO registry. *Arthritis Rheum* 2011;63:382–90.
22 Thomas ML, Shaddick G, Charlton R, *et al*. Tumor necrosis factor inhibitor monotherapy versus combination therapy for the treatment of psoriatic arthritis: combined analysis of European biologics databases. *J Rheumatol* 2021;48:48–57.

CLINICAL SCIENCE

Effectiveness of IL-12/23 inhibition (ustekinumab) versus tumour necrosis factor inhibition in psoriatic arthritis: observational PsABio study results

Josef S Smolen ,[1] Stefan Siebert,[2] Tatiana V Korotaeva,[3] Carlo Selmi ,[4] Paul Bergmans,[5] Elisa Gremese,[6] Beatriz Joven-Ibáñez,[7] Gkikas Katsifis,[8] Wim Noël,[9] Michael T Nurmohamed,[10] Pascal Richette ,[11,12] Petros P Sfikakis ,[13] Kurt de Vlam,[14,15] Elke Theander,[16] Laure Gossec [17,18]

Handling editor David S Pisetsky

► Additional online supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220263).

For numbered affiliations see end of article.

Correspondence to
Dr Josef S Smolen, Medical University of Vienna, 1090 Wien, Austria;
josef.smolen@meduniwien.ac.at

Received 2 March 2021
Accepted 27 May 2021
Published Online First 23 June 2021

ABSTRACT

Objectives To evaluate 6-month effectiveness of ustekinumab versus tumour necrosis factor inhibitor (TNFi), analysing predictors of low disease activity (LDA)/remission.

Methods PsABio is a prospective, observational cohort study of patients with psoriatic arthritis (PsA) at 92 sites in eight European countries, who received first-line to third-line ustekinumab or a TNFi. Comparative achievement at 6 months of clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) LDA/remission, and minimal disease activity (MDA)/very LDA using propensity score (PS)-adjusted multivariate logistic regression was assessed.

Results In the final analysis set of 868 participants with 6-month follow-up data (ustekinumab, n=426; TNFi, n=442), with long-standing disease and a high mean cDAPSA score (31.0 vs 29.8, respectively), proportions of patients in ustekinumab/TNFi treatment groups achieving cDAPSA LDA at 6 months were 45.7%/50.7%. cDAPSA remission was achieved in 14.9%/19.2%, and MDA in 26.4%/30.8% of patients. PS-adjusted odds ratios (OR; 95% confidence interval (CI)) of reaching cDAPSA LDA and MDA were 0.73 (0.46 to 1.15) and 0.87 (0.61 to 1.25) with ustekinumab versus TNFi, indicating no significant difference. High baseline body mass index or high cDAPSA were associated with a lower chance (OR (95% CI)) of reaching cDAPSA LDA with TNFi (0.94 (0.89 to 0.99) and 0.64 (0.52 to 0.79), respectively). Predictive factors were similar to previously published evidence, with cDAPSA and 12-item Psoriatic Arthritis Impact of Disease scores and chronic widespread pain at baseline appearing as new risk factors for unfavourable outcome. Safety data were similar between groups.

Conclusion Treatment targets were reached similarly after 6 months of treatment with ustekinumab and TNFi.

Key messages

What is already known about this subject?

- Psoriatic arthritis (PsA) is a heterogeneous disease, and randomised controlled trials (RCTs) may not adequately represent patients receiving a biologic in clinical practice.
- Treatment decisions can be challenging in PsA because of the variety of available drugs, and although efficacy and safety have been demonstrated in RCTs, real-world data comparing biologics are limited.

What does this study add?

- The PsABio study provides real-world observational data on outcomes of patients starting treatment with either ustekinumab or tumour necrosis factor inhibitors.

How might this impact on clinical practice or future developments?

- The PsABio study provides comparative data to help inform treatment decisions in clinical practice.
- Information on previously known and potential new negative predictors of treatment response in patients with PsA may help inform patient prognosis.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic immune-mediated disease that affects approximately 20%–30% of patients with psoriasis.[1 2] PsA has a variable disease course, and may present with a combination of peripheral and axial disease signs, including arthritis, enthesitis, dactylitis and skin and nail manifestations. Current treatment options include non-steroidal anti-inflammatory drugs (NSAIDs); conventional synthetic disease-modifying antirheumatic drugs (csDMARDs); targeted synthetic DMARDs (tsDMARDs) and biological DMARDS (bDMARDs).[3 4]

The interleukin (IL)-12 and IL-23/IL-17 axes are implicated as significant pathways in disease pathogenesis.[5–7] A number of bDMARDs directed against IL-12/IL-23, IL-17 or IL-23 are now available to treat PsA, alongside tumour necrosis factor inhibitors (TNFi).[8] The IL-12/23 axis can be inhibited with ustekinumab, a fully human immunoglobulin G1 monoclonal antibody that blocks the p40 subunit shared by these two cytokines.[5 9] Two phase 3, placebo-controlled trials—PSUMMIT 1[10] and PSUMMIT 2[11]—demonstrated ustekinumab efficacy on joints and skin, and safety in patients with PsA.

Treatment decisions are challenging in PsA, given the wide array of available drugs, and the scarcity

To cite: Smolen JS, Siebert S, Korotaeva TV, *et al*. *Ann Rheum Dis* 2021;**80**:1419–1428.

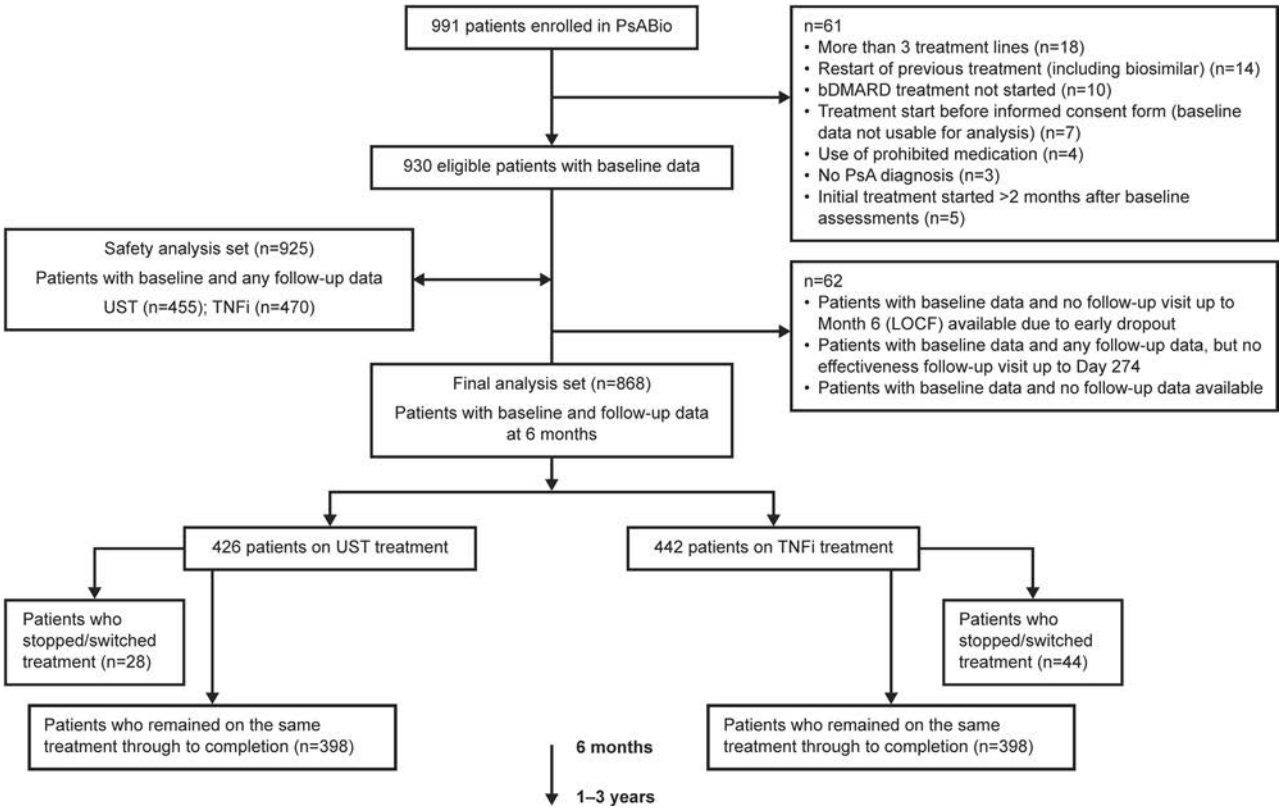


Figure 1 Patient population flow diagram. The FAS included patients who completed the 6-month initial treatment, as well as those who switched/stopped their original treatment during the 6-month follow-up period. Patients who switched/stopped their biological disease-modifying antirheumatic drug were imputed as non-responders. bDMARD, biological disease-modifying antirheumatic drug; FAS, final analysis set; LOCF, last observation carried forward; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

of head-to-head trials of biologics.[12–14] Although clinical trials provide important information on drug efficacy and safety, real-world patient populations may not fully represent those in clinical practice.[15] There are currently no published studies in PsA comparing ustekinumab and TNFi effectiveness in a large-cohort, real-world setting. Such data are important for making evidence-based treatment decisions in clinical practice.

The ultimate goal of PsA treatment is to achieve the lowest disease activity possible, defined by several composite measures, the most widely used being the clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) and minimal disease activity/very low disease activity (MDA/VLDA).[3 16–18] Here, we present the first real-world comparative 6-month effectiveness study for ustekinumab versus TNFi.

METHODS

Study design

PsABio (NCT02627768) is an international, prospective, observational, cohort study designed to evaluate the persistence, effectiveness and tolerability of ustekinumab versus TNFi as a first-line, second-line or third-line bDMARD in PsA. Each patient is followed biannually for up to 3 years, with a first analysis performed once all patients have reached the 6-month time point (figure 1). Outcomes are focused on achievement of cDAPSA low disease activity (LDA)/remission and MDA/VLDA and analysing predictors of reaching cDAPSA LDA or MDA.

Patients

Participants were enrolled between December 2015 and June 2018, at 92 sites in Belgium, France, Greece, Italy, the Netherlands, the Russian Federation, Spain and the UK, and treated according to standard clinical practice. The choice of bDMARD was made independently by each patient's rheumatologist; TNFi choice was at the investigator's discretion.

Adult patients with PsA, according to the ClASsification for Psoriatic ARthritis (CASPAR) criteria,[19] starting ustekinumab or any approved TNFi (including biosimilars; online supplemental table S1) as a first-line, second-line or third-line bDMARD therapy for PsA (online supplemental table S2), were included. All participants with baseline and effectiveness data, available between baseline and the 6-month (±3 months) follow-up (including patients who switched/stopped treatment due to adverse events (AEs), inefficacy or other reasons), were included in this analysis.

Patients were excluded if they were treated beyond third line, had received an investigational drug, vaccine or invasive medical device within 30 days before study start, or were currently enrolled in an interventional study.

Data were collected at baseline, then every 6 months with a window of ±3 months for flexibility with standard clinical practice. Data came from patients' medical records, including available patient-reported outcomes data, and were collected and entered into an electronic case report form, except for physician-reported and investigator-reported scales/assessments, which were recorded on paper forms. Patients who stopped/switched ustekinumab or TNFi were retained and followed up on their new treatment (another TNFi or bDMARD, or a csDMARD or tsDMARD, or no additional therapy). In total, 991 patients entered the study; 477 started ustekinumab, 501 started TNFi, 10 did not start either treatment, and three were not diagnosed

with PsA. Another 48 patients were excluded from the analysis owing to protocol violations (figure 1).

Evaluations

Treatment effectiveness

The following data were recorded for both ustekinumab and TNFi to allow comparison of effectiveness at 6 months. PsABio focused on the composite disease activity measures cDAPSA LDA and remission,[17 20] and achievement of MDA and VLDA.[21] cDAPSA is based on the summation of four variables: tender joint count of 68 joints (TJC68), swollen joint count of 66 joints (SJC66), Patient Global Assessment (PtGA) visual analogue scale (VAS, in cm) and patient pain (PtP) VAS. cDAPSA LDA is defined as a score of ≤13, and cDAPSA remission as a score of ≤4.[17] The MDA/VLDA criteria assess seven domains (cut-offs): TJC68 (≤1); SJC66 (≤1); enthesitis (Leeds Enthesitis Index[22]; ≤1); skin involvement (Psoriasis Area and Severity Index [≤1] or psoriasis body surface area [BSA; ≤3%]); Health Assessment Questionnaire (HAQ) score (≤0.5); PtGA VAS (≤20, VAS in mm); and PtP VAS (≤15). If five of seven domain cut-offs are met, MDA has been achieved; VLDA if all seven are met.

Data were also collected for the following variables: Physician Global Assessment (PGA) VAS for disease activity; the presence of dactylitis; and psoriasis skin involvement (BSA according to four categories (clear/almost clear skin, <3% but not clear/almost clear skin, 3%–10% and >10%)).

Patient-reported outcomes and assessments

Aside from those needed for the MDA/VLDA and cDAPSA, additional patient-reported outcomes were collected (see online supplemental methods).

Safety

Safety data included collection of reported AEs and serious AEs from the first use of ustekinumab or a TNFi in the study.

Statistical analyses

Data validation, development of a detailed analysis plan and all statistical analyses were performed by or under the authority of the sponsor (Janssen Pharmaceutica NV, Beerse). In this analysis, the full analysis set (FAS) included patients who completed the 6-month initial treatment period, plus those who switched/stopped their original treatment during the 6-month follow-up. The safety set included all patients with baseline and any available follow-up data. Partially missing data were imputed where required for analysis. For validated scales, missing items were imputed according to recommendations of the scale developers. Percentages were calculated over non-missing data. In addition to observed case analysis, endpoint analysis used the last observation carried forward (LOCF). Actual values and changes from baseline were summarised, including the 95% CI, at each assessment time point and at LOCF.

As the analysis was exploratory, no predefined hypotheses were tested and no adjustment for multiplicity was applied. Hence, between-group differences and changes over time were described using the 95% confidence interval (CI) rather than by p values, as the latter provide no information about the variability of an estimated association.[23]

Comparative effectiveness and predictor analyses were performed to investigate LOCF month 6 outcomes between and within treatment cohorts. Comparative effectiveness was also described by bDMARD treatment line. Patients who switched/stopped their original treatment during the 6-month follow-up period were imputed as non-responders (binary endpoints), or no improvement from baseline (continuous endpoints). Patients with cDAPSA LDA included those in cDAPSA remission; patients in MDA included those in VLDA.

Comparative effectiveness between treatment cohorts included propensity score (PS) adjustment for imbalanced baseline covariates. For all potential confounders, the balance between the treatment cohorts and the prognostic effect on the outcome of interest were investigated. The PS was estimated using a logistic regression model, with treatment as the dependent variable and a set of potential confounders as independent variables. After optimisation to achieve a good balance of all confounders, the PS, stratified on the quintiles, was used to estimate the adjusted treatment effects for the selected outcomes. Weighting on the PS (inverse probability of treatment weighting) was used as a sensitivity analysis. Primarily based on clinical judgement and published evidence, the following potential baseline confounders were investigated: age, sex, country, smoking, number of comorbidities, BSA, PsA subtype according to Moll and Wright criteria,[24] disease duration, cDAPSA score, 12-item Psoriatic Arthritis Impact of Disease (PsAID-12) score, presence of enthesitis or dactylitis, Fibromyalgia Rapid Screening Tool (FiRST) score, line of bDMARD treatment, csDMARD cotreatment and concomitant NSAID or oral corticosteroid use.

The predictor analyses investigated possible predictors for achieving cDAPSA, LDA and MDA outcomes. The effect of all variables was first investigated using univariate analysis. Variables with $p \leq 0.5$ were then included in multiple logistic regression analysis, using a forward selection method with the probability for variable entry set to $p=0.20$, including the examination of interaction terms. Six different models were generated: total group, and ustekinumab and TNFi cohorts, respectively, for cDAPSA LDA/remission and MDA/VLDA. The final multivariate model with odds ratios (ORs; 95% CI) is presented for factors with significant ($p<0.05$) effect on the respective outcome separately for the total, ustekinumab and TNFi cohorts.

In addition to the analysis on the FAS discussed in this paper, a completer analysis was performed, including only patients who stayed on ustekinumab or a TNFi for the entire 6-month follow-up period. The completer analysis, which arrived at similar results, is presented in online supplemental table S3.

RESULTS

Patient disposition

Of 991 enrolled participants, 930 were eligible and had baseline data (figure 1); 62 were not included in the FAS owing to unavailability of effectiveness data.

The FAS comprised 868 patients for whom both baseline and follow-up data to month 6 were available (426 ustekinumab, 442 TNFi), including 28 (6.6%) patients who switched/stopped ustekinumab and 44 (10.0%) who switched/stopped TNFi during the first 6-month period. The completer analysis set comprised 796 patients (online supplemental table S3). The safety analysis set comprised 455 patients in the ustekinumab group and 470 in the TNFi group (n=925 with follow-up data; figure 1).

Baseline demographics and clinical characteristics

At baseline, participants in the ustekinumab group were significantly older compared with the TNFi group (mean age, 51.2 vs 48.5 years, respectively; based on 95% CI), had significantly longer disease duration (mean, 7.5 vs 6.2 years) and more extensive use of third-line bDMARDs (20.4% vs 12.0%), but less frequent ongoing csDMARD exposure (39.2 vs 54.5%),

Table 1 Demographics at baseline

	UST (n=426)	TNFi (n=442)
Age, years (95% CI)	51.2 (12.47) (**50.0 to 52.3**)	48.5 (12.59) (**47.3 to 49.7**)
Sex—male, n (%) (95% CI)	183 (43.0) (38.2 to 47.8)	202 (45.7) (41.0 to 50.5)
Disease duration since initial diagnosis, years (95% CI)	7.5 (8.1) (**6.8 to 8.3**)	6.2 (6.6) (**5.6 to 6.8**)
BMI, kg/m^2 (95% CI)	28.6 (6.3) (27.9 to 29.3)	27.7 (5.0) (27.2 to 28.3)
csDMARD exposure, n (%) (95% CI)		
Previous exposure	376 (88.3) (84.8 to 91.2)	411 (93.0) (84.8 to 91.2)
Ongoing exposure at baseline	167 (39.2) (**34.5 to 44.0**)	241 (54.5) (**49.8 to 59.2**)
Methotrexate exposure ongoing at baseline, n (%) (95% CI)	127 (29.8) (**25.5 to 34.4**)	187 (42.3) (**37.7 to 47.1**)
Other treatments exposure ongoing at baseline, n (%) (95% CI)		
NSAIDs	232 (54.5) (**49.6 to 59.3**)	307 (69.5) (**64.9 to 73.7**)
Glucocorticosteroids	138 (32.4) (28.0 to 37.1)	152 (34.4) (30.0 to 39.0)
Line of bDMARD treatment, n (%) (95% CI)		
First line	193 (45.3) (40.5 to 50.2)	241 (54.5) (49.8 to 59.2)
Second line*	146 (34.3) (29.8 to 39.0)	148 (33.5) (29.1 to 38.1)
Third line*	87 (20.4) (**16.7 to 24.6**)	53 (12.0) (**9.1 to 15.4**)
Cardiovascular/metabolic syndrome comorbidity, n (%) (95% CI)†	176 (41.3) (36.6 to 46.2)	157 (35.5) (31.1 to 40.2)

Data are mean (SD) (95% CI of the mean) unless otherwise stated; % is that of available data. Numbers in bold indicate where significant differences exist at baseline.
*bDMARDs received before UST/TNFi in this study are presented in online supplemental table S2.
†Cardiovascular/metabolic syndrome comorbidity was numerically more frequent in the UST group.
bDMARD, biological disease-modifying antirheumatic drug; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

concomitant methotrexate (29.8% vs 42.3%) and NSAIDs (54.5% vs 69.5%) (table 1). Severe skin involvement (BSA >10%, 26.7% vs 14.1%) and FiRST score ≥5 (indicating more chronic widespread pain: 39.3% vs 29.0%) were significantly more prevalent in the ustekinumab group (table 2). Cardiovascular/metabolic comorbidities (41.3% vs 35.5%) were also numerically more frequent in the ustekinumab group (table 1).

Components of cDAPSA and MDA at baseline and 6 months

Observed data at baseline and for changes at 6-month follow-up (including LOCF) for the components needed to assess cDAPSA and MDA are presented in table 3. No difference was shown between the ustekinumab and TNFi groups in improvements in SJCs and TJCs, HAQ-Disability Index scores, VAS assessments of global well-being (PtGA, and PGA) and change in BSA (demonstrated by overlapping 95% CI) (table 3).

Change from baseline in composite disease activity measures

At baseline, mean (95% CI) cDAPSA levels in the ustekinumab and TNFi groups were 31.0 (28.9 to 33.1) and 29.8 (27.9 to 31.7), respectively, indicating high disease activity in both treatment groups (table 2). The mean (95% CI) change in cDAPSA from baseline at 6 months was −13.7 (−15.5 to −11.8) and −14.5 (−16.2 to −13.0), respectively. The proportions of patients achieving cDAPSA LDA (including remission) were 177/360 (49.2%; 43.9 to 54.5) vs 200/370 (54.1%; 48.8 to 59.2), cDAPSA remission 63/360 (17.5%;

Table 2 PsA clinical characteristics at baseline

	UST (n=426)	TNFi (n=442)
Psoriasis BSA, n (%) (95% CI)		
Clear/almost clear skin	99 (28.8) (24.1 to 33.9)	123 (34.1) (29.2 to 39.2)
<3% but not clear/almost clear skin	33 (9.6) (6.7 to 13.2)	58 (16.1) (12.4 to 20.3)
3%–10%	120 (34.9) (29.9 to 40.2)	129 (35.7) (30.8 to 40.9)
>10%	92 (26.7) (**22.1 to 31.8**)	51 (14.1) (**10.7 to 18.2**)
PsA characteristics, n (%) (95% CI)		
Axial involvement—pure or combined with peripheral	147 (35.4) (30.8 to 40.2)	161 (37.2) (32.6 to 41.9)
Oligoarticular	93 (22.4) (18.5 to 26.7)	125 (28.9) (24.6 to 33.4)
Polyarticular	277 (66.7) (62.0 to 71.3)	280 (64.7) (60.0 to 69.2)
Swollen joint count—66 joints (95% CI)	6.0 (8.1) (5.2 to 6.8)	5.8 (7.4) (5.1 to 6.5)
Tender joint count—68 joints (95% CI)	12.5 (12.5) (11.2 to 13.7)	11.3 (10.8) (10.3 to 12.4)
cDAPSA (95% CI)	31.0 (20.3) (28.9 to 33.1)	29.8 (18.6) (27.9 to 31.7)
Enthesitis at baseline, n (%) (95% CI)	199 (48.9) (43.9 to 53.9)	218 (51.9) (47.0 to 56.8)
Dactylitis at baseline, n (%) (95% CI)	80 (18.8) (15.2 to 22.9)	92 (20.8) (17.1 to 24.9)
Total PsAID-12 score (95% CI)	5.7 (2.2) (5.5 to 5.9)	5.5 (2.1) (5.3 to 5.7)
FiRST score ≥5, n (%) (95% CI)	160 (39.3) (**34.5 to 44.2**)	121 (29.0) (**24.7 to 33.6**)
ACPA positive, n (%) (95% CI)	3.0 (3.2) (0.7 to 9.1)	4.0 (2.9) (0.8 to 7.2)
RF positive, n (%) (95% CI)	3.0 (2.1) (0.4 to 5.9)	11 (5.8) (2.9 to 10.1)
CRP, mg/dL	1.3 (3.0) (1.0 to 1.7)	1.6 (2.9) (1.2 to 1.9)

Data are mean (SD) (95% CI of the mean) unless otherwise stated; % is that of available data. Numbers in bold indicate where significant differences exist at baseline.
ACPA, anti-citrullinated protein antibody; BSA, body surface area; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; CRP, C-reactive protein; FiRST, Fibromyalgia Rapid Screening Tool; PsA, psoriatic arthritis; PsAID-12, 12-item Psoriatic Arthritis Impact of Disease questionnaire; RF, rheumatoid factor; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

Table 3 Change in PSA outcome variables needed for assessing cDAPSA and MDA

Variable	UST Baseline	TNFi Baseline	UST Change at 6 months	TNFi Change at 6 months
cDAPSA	31.0 (28.9 to 33.1)	29.8 (27.9 to 31.7)	−13.7 (−15.5 to −11.8)	−14.6 (−16.2 to −13.0)
Tender joint count—68 joints	12.5 (11.2 to 13.7)	11.3 (10.3 to 12.4)	−5.3 (−6.4 to −4.2)	−5.7 (−6.6 to −4.8)
Swollen joint count—66 joints	6.0 (5.2 to 6.8)	5.8 (5.1 to 6.5)	−3.7 (−4.4 to −3.0)	−3.7 (−4.4 to −3.1)
HAQ-DI assessment	1.1 (1.1 to 1.2)	1.2 (1.1 to 1.2)	−0.25 (−0.3 to −0.2)	−0.34 (−0.4 to −0.3)
Physician Global Assessment of Disease—VAS, mm	53.5 (51.6 to 55.3)	54.7 (52.7 to 56.6)	−23.3 (−25.7 to −20.8)	−24.9 (−27.3 to −22.6)
Patient Global Assessment of Disease— VAS, mm	61.1 (58.8 to 63.5)	61.1 (58.7 to 63.4)	−20.7 (−23.5 to −18.0)	−25.2 (−28.2 to −22.3)
Patient assessment of pain—VAS*, mm	60.6 (58.1 to 63.0)	61.2 (58.9 to 63.5)	−19.1 (−21.9 to −16.2)	−24.4 (−27.2 to −21.6)
Total enthesitis score (LEI)	2.6 (2.4 to 2.8)	2.6 (2.4 to 2.8)	−1.4 (−1.6 to −1.2)	−1.5 (−1.7 to −1.2)
Psoriasis BSA distribution, n (%) (95% CI)				
Clear/almost clear skin	99 (28.8) (24.1 to 33.9)	123 (34.1) (29.2 to 39.2)	312 (59.1) (54.8 to 63.3)	335 (63.6) (59.3 to 67.7)
<3% but not clear/almost clear	33 (9.6) (6.7 to 13.2)	58 (16.1) (12.4 to 20.3)	70 (13.3) (10.5 to 16.5)	85 (16.1) (13.1 to 19.6)
3%–10%	120 (34.9) (29.9 to 40.2)	129 (35.7) (30.8 to 40.9)	133 (25.2) (21.5 to 29.1)	93 (17.6) (14.5 to 21.2)
>10%	92 (26.7) (22.1 to 31.8)	51 (14.1) (10.7 to 18.2)	13 (2.5) (1.3 to 4.2)	14 (2.7) (1.5 to 4.4)
Psoriasis BSA improvement† from baseline, n (%)	–	–	184 (53.5) (48.1 to 58.9)	166 (46.0) (40.8 to 51.3)

Data are observed mean (95% CI) at month 6 (last observation carried forward), unless otherwise indicated.
*There was a significantly higher percentage of UST patients with chronic widespread pain (FiRST score).
†Improvement: at least one category.
BSA, body surface area; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; HAQ-DI, Health Assessment Questionnaire Disability Index; LEI, Leeds Enthesitis Index; MDA, minimal disease activity; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab; VAS, visual analogue scale.

13.7 to 21.8) vs 81/370 (21.9%; 17.8 to 26.5), MDA 104/385 (27.0%; 22.6 to 31.7) vs 120/376 (31.9%; 27.2 to 36.9), and VLDA 34/410 (8.3%; 5.8 to 11.4) vs 38/395 (9.6%; 6.9 to 13.0) at 6 months in the ustekinumab and TNFi groups, respectively (figure 2A). The PS-adjusted ORs of ustekinumab versus TNFi for achieving cDAPSA LDA/remission, MDA or VLDA indicated similar effectiveness (figure 2B). The outcomes observed in the FAS and completer sets were similar to those observed in the main analysis (online supplemental table S4). Composite disease activity measures by treatment line are shown in figure 3.

Predicting a state of cDAPSA LDA or MDA

Baseline variables and treatment group (ustekinumab or TNFi) were investigated as predictors of response, defined as reaching cDAPSA LDA or MDA by month 6 of follow-up. Treatment with either therapy (mode of action) was not associated with any of the model outcomes. Table 4 presents results from the final model, illustrating that previously described negative predictors of good treatment response are confirmed in the total PsABio cohort (eg, line of treatment, female sex, comorbidities),[25–28] but also new potential negative predictors are identified, such as high baseline impact of disease activity (PsAID-12) or high baseline cDAPSA or FiRST score.[29 30] Exposure to oral glucocorticosteroids also decreased the odds.

Higher body mass index (BMI) and higher cDAPSA at baseline did not significantly affect these treatment outcomes in the ustekinumab cohort in contrast to the TNFi cohort, where higher BMI acted as a negative predictor. Enthesitis appeared as a negative factor in the ustekinumab cohort only, dactylitis as a positive predictor for MDA in the TNFi cohort. Female sex did not significantly impair the response to TNFi, as it did in the ustekinumab cohort. Generally, the differences between the cohorts were small, and differences compared with the total cohort were mainly due to lower statistical power (table 4).

Concomitant treatment with csDMARDs/methotrexate was not associated with higher likelihood of cDAPSA LDA or MDA in either cohort.

Changes from baseline in health-related quality of life

Figure 4A shows the changes from baseline to month 6 in health state from EuroQoL 5-dimension 3-level questionnaire (EQ5D-3L) score (ustekinumab: +8.6 (95% CI 5.9 to 11.2), TNFi: +11.8 (95% CI 9.0 to 14.6)) and PsAID-12 score (ustekinumab: −1.8 (95% CI −2.04 to −1.59), TNFi: −1.9 (95% CI −2.13 to −1.69)). For both the ustekinumab and TNFi groups, achievement of cDAPSA remission/LDA or MDA at 6 months was associated with significant and clinically relevant improvement in EQ5D-3L, VAS and PsAID-12 scores, and thus impact of the disease on patients' lives (figure 4B).

Adverse events

Safety data were similar between the ustekinumab and TNFi groups; 17.9% of patients in the ustekinumab and 20.9% in the TNFi group experienced at least one AE, and 3.5% and 1.6%, respectively, experienced at least one serious AE (online supplemental table S5).

DISCUSSION

The observational PsABio study provides important information on the efficacy of ustekinumab and TNFi in a real-world cohort of patients with PsA; study data indicated similar effectiveness for ustekinumab and TNFi. PsABio demonstrated that approximately half of all patients but also half of those patients in whom previous therapies had an insufficient response and who received UST or TNFi as second- or third-line treatments, can achieve cDAPSA LDA, with many also reaching MDA or remission.

The question of how biologics other than TNFi perform in routine care remains unanswered, and the PsABio study aims to address this. In the current analysis, we have shown that overall and unadjusted, 28% of patients on ustekinumab achieved the goal of MDA at 6 months compared with 32% of patients receiving a TNFi. This compares with 30%–71% of patients in previous smaller real-world studies of ustekinumab,[31–35] 50%–60% of TNFi-treated patients,[5] and 11%–34% of patients with PsA in placebo-controlled Phase 3 studies of biological therapies.[14 36–39] After PS adjustment for imbalances in potential baseline confounders, both TNFi and ustekinumab had

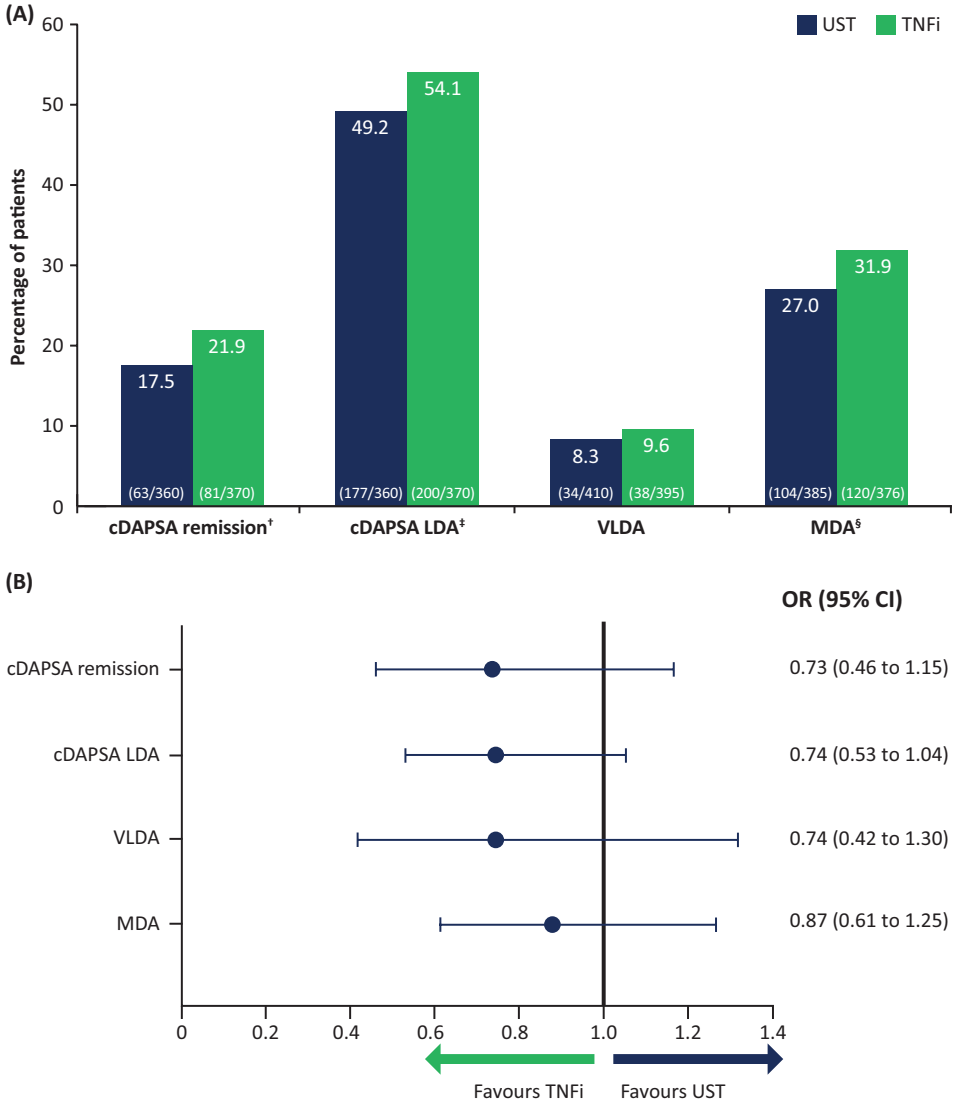


Figure 2 Disease outcomes at month 6 (A) observed percentages*; (B) PS-adjusted ORs (95% CI) of ustekinumab versus TNFi outcomes. *Observed percentages including non-responder imputation of patients who stopped or switched initial treatment. †cDAPSA remission ≤4. ‡Including remission; cDAPSA ≤13. §Including VLDA. cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; LDA, low disease activity; MDA, minimal disease activity; PS, propensity score; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab; VLDA, very low disease activity.

a comparable effect on disease activity measures, including achievement of MDA, cDAPSA-LDA and change in cDAPSA.[40] In PsABio, participants in the ustekinumab group were more often receiving it as third-line biologic, and were older than the TNFi group, with longer disease duration. Additionally, a higher proportion of patients had more severe skin involvement, comorbidities or chronic widespread pain. Based on these baseline characteristics, the ustekinumab group could be regarded as more refractory to treatment than the TNFi comparison group which reduces the likelihood of a good response; prespecified PS adjustment for the baseline differences was performed for a fair statistical comparison between groups.

While the predictors of treatment success in our study generally agree with previous publications for TNFi (eg, line of treatment, female sex, comorbidities),[25–28] we highlight some new and modifiable negative predictors, such as high disease impact (PsAID-12) and high clinical disease activity as well as signs of chronic, widespread pain. These results reflect the complex and multifactorial influences on the outcomes with treatment. Effective early intervention may avoid the evolution of patients' disease towards these unfavourable states. Generally, ustekinumab and TNFi effectiveness are predicted by similar factors with some exceptions, such as higher BMI, higher cDAPSA and chronic widespread pain, negatively influencing mainly TNFi but not ustekinumab, while TNFi did not seem to be impacted by female sex, cardiovascular comorbidities or enthesitis, in contrast to ustekinumab.

Previous studies reported that 30%–60% of patients treated with biological therapy achieved a state of remission/LDA or MDA.[29 30 32] Moreover, there is evidence that earlier-stage treatment for PsA can result in more patients achieving remission.[41] Approximately half of patients in PsABio achieved LDA, with associated improvement in quality of life and disease impact.

The present analysis has several strengths and limitations. Here, 6-month data are presented; additional publications at later follow-up will provide further information on longer-term effectiveness, persistence and safety. A recent paper pointed towards high rates of persistence, LDA and remission in PsA patients on TNFi after 1 and 12 years of follow-up. Our long-term data will complement these results.[42] A strength of PsABio is that it consists

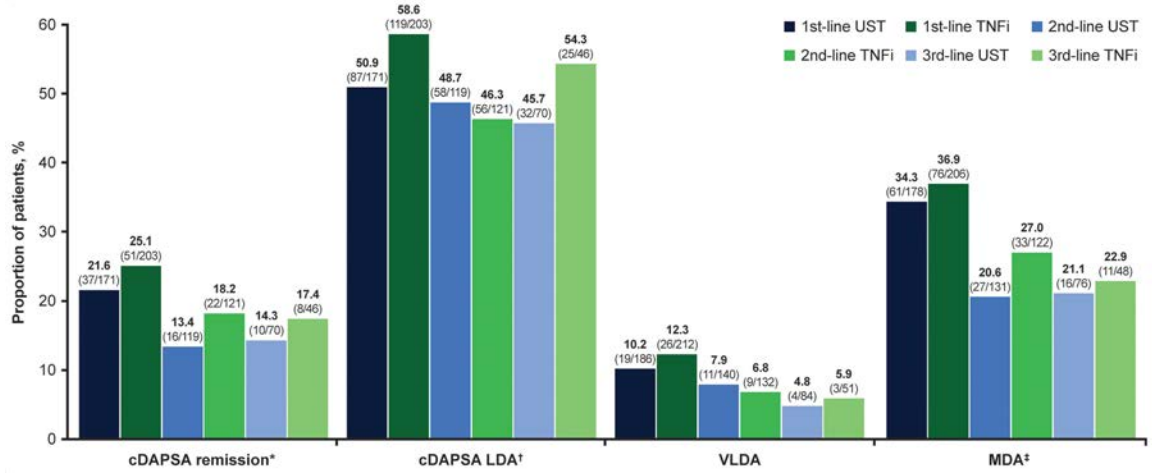


Figure 3 Disease outcomes at month 6 (observed percentages). Observed percentages (intention-to-treat analysis set) including non-responder imputation. *cDAPSA remission ≤4. †Including remission; cDAPSA ≤13. ‡Including VLDA. cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; LDA, low disease activity; MDA, minimal disease activity; PS, propensity score; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab; VLDA, very low disease activity.

of a large, prospectively followed population with PsA receiving bDMARDs with two different modes of action. The real-world nature of PsABio also has the advantage of providing data from a less tightly selected patient population than randomised controlled trials.[15] However, as PsABio is non-randomised, the treatment groups need to be balanced using PS adjustment, owing to documented confounding data or bias by the rheumatologists' selection strategies. A potential limitation of this is that PS matching may not succeed in fully adjusting for unknown or unmeasured differences in baseline characteristics.[43]

An inherent problem in the present study is confounding by indication, occurring when the indication to prescribe a particular treatment is based on the severity of the illness or associated disease characteristics including multimorbidity.[44] Baseline findings of later biologic use, more severe skin involvement and more chronic widespread pain (FiRST score ≥5) in

Table 4 Factors associated with reaching the treatment targets of MDA and cDAPSA LDA, in the total PsABio cohort and in the ustekinumab cohort and TNFi cohort

	Total cohort		Ustekinumab cohort		TNFi cohort	
Test variable (baseline state)	**MDA**	**cDAPSA LDA**	**MDA**	**cDAPSA LDA**	**MDA**	**cDAPSA LDA**
No of patients, n*	621	614	315	306	306	308
Coefficient of determination, R^2	0.32	0.32	0.36	0.36	0.35	0.35
Line of bDMARD: first-line versus second-/third-line	1.69 (1.13 to 2.53)	1.23 (0.84 to 1.78)	1.83 (1.02 to 3.29)	0.87 (0.50 to 1.50)	1.78 (0.99 to 3.22)	1.78 (1.02 to 3.09)
Sex: female versus male	0.50 (0.33 to 0.75)	0.60 (0.41 to 0.88)	0.34 (0.19 to 0.63)	0.40 (0.22 to 0.70)	0.58 (0.31 to 1.06)	0.80 (0.45 to 1.41)
CV comorbidity/metabolic syndrome: present versus not present	0.49 (0.32 to 0.76)	0.63 (0.42 to 0.93)	0.44 (0.23 to 0.83)	0.47 (0.26 to 0.84)	0.54 (0.30 to 1.00)	0.80 (0.46 to 1.41)
Body mass index: per 1 kg/m^2	0.97 (0.94 to 1.01)	0.97 (0.93 to 0.99)	0.97 (0.91 to 1.03)	0.99 (0.94 to 1.04)	0.98 (0.93 to 1.04)	0.94 (0.89 to 0.99)
cDAPSA: per 10 score unit higher	0.75 (0.64 to 0.88)	0.75 (0.66 to 0.85)	0.89 (0.73 to 1.08)	0.86 (0.72 to 1.02)	0.58 (0.44 to 0.76)	0.64 (0.52 to 0.79)
PsAID-12 score: per one score unit higher	0.86 (0.77 to 0.97)	0.87 (0.79 to 0.97)	0.84 (0.71 to 0.99)	0.82 (0.69 to 0.96)	0.88 (0.74 to 1.03)	0.92 (0.79 to 1.07)
Enthesitis: present at baseline versus not present	0.60 (0.40 to 0.92)	0.57 (0.38 to 0.84)	0.32 (0.17 to 0.62)	0.43 (0.24 to 0.78)	1.23 (0.66 to 2.27)	0.83 (0.47 to 1.49)
Dactylitis: present at baseline versus not present	1.05 (0.64 to 1.74)	1.16 (0.72 to 1.86)	0.56 (0.25 to 1.23)	0.64 (0.31 to 1.32)	2.15 (1.04 to 4.45)	2.01 (0.99 to 4.04)
Psoriasis body surface area						
<3% vs 3%–10%	0.89 (0.57 to 1.41)	1.66 (1.08 to 2.56)	1.17 (0.59 to 2.33)	2.08 (1.09 to 3.97)	0.61 (0.32 to 1.16)	1.33 (0.71 to 2.47)
<3% vs >10%	0.70 (0.40 to 1.24)	1.49 (0.88 to 2.52)	1.26 (0.57 to 2.78)	2.32 (1.11 to 4.84)	0.33 (0.13 to 0.86)	0.95 (0.42 to 2.17)
NSAID treatment: yes versus no	0.65 (0.42 to 1.01)	0.73 (0.49 to 1.09)	0.84 (0.40 to 1.74)	0.77 (0.41 to 1.45)	0.61 (0.34 to 1.12)	0.64 (0.37 to 1.11)
Use of oral corticosteroids: yes versus no	0.50 (0.27 to 0.92)	0.47 (0.27 to 0.80)	0.51 (0.21 to 1.25)	0.40 (0.16 to 0.86)	0.45 (0.19 to 1.08)	0.49 (0.23 to 1.03)
FiRST score: per unit increase	0.88 (0.78 to 0.98)	0.85 (0.77 to 0.95)	0.85 (0.72 to 1.00)	0.86 (0.74 to 1.00)	0.88 (0.74 to 1.05)	0.82 (0.70 to 0.96)

Data are OR (95% CI) unless otherwise stated.
*The n for the cohorts indicate the number of patients included in the respective model. Numbers are lower than total UST or TNFi patient cohorts due to missing variable data, such as missing patient-reported outcomes and skin assessments in some patients.
bDMARD, biological disease-modifying antirheumatic drug; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; CV, cardiovascular; FiRST, Fibromyalgia Rapid Screening Tool; LDA, low disease activity; MDA, minimal disease activity; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; PsAID-12, 12-item Psoriatic Arthritis Impact of Disease questionnaire; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

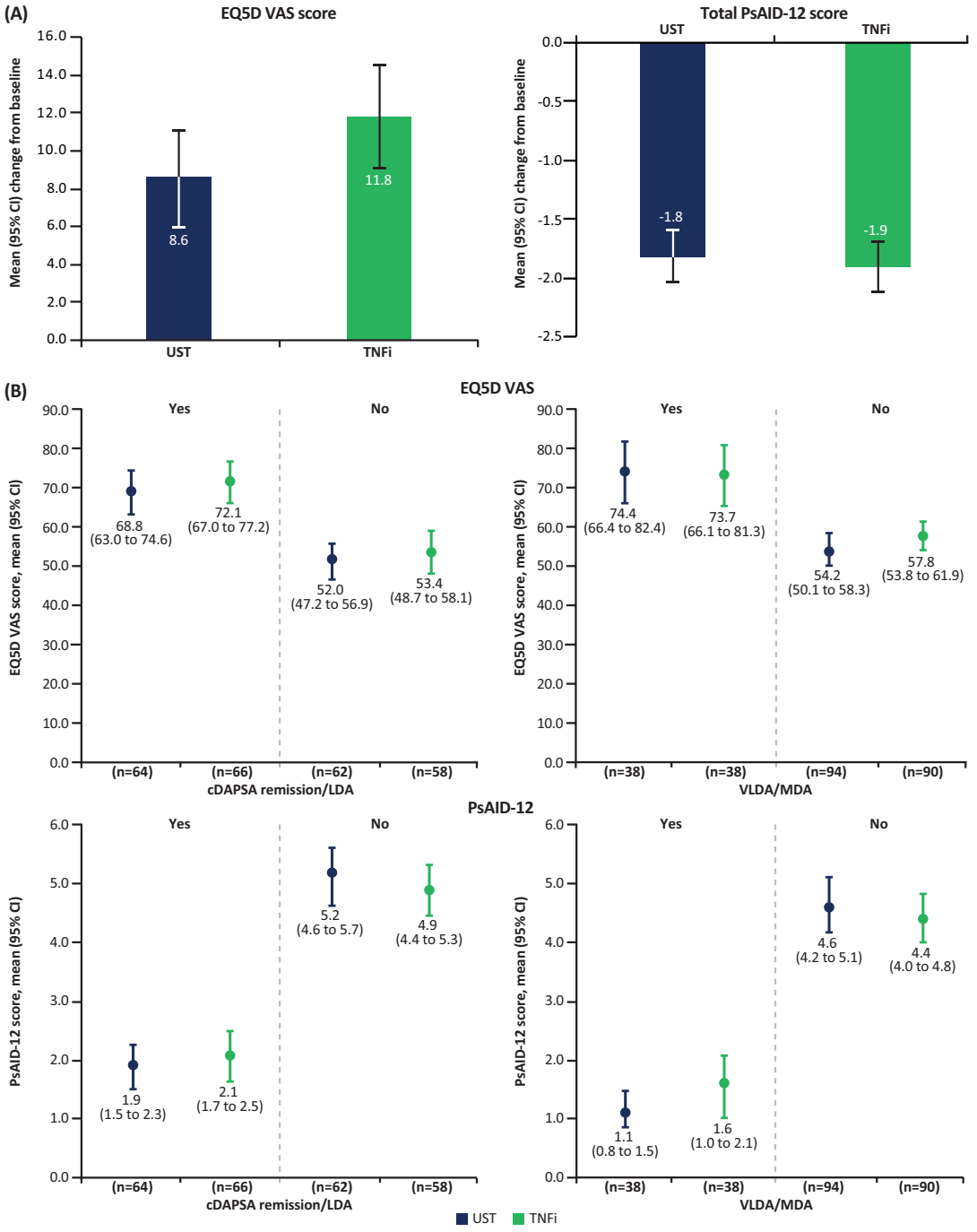


Figure 4 Efficacy of ustekinumab and TNFi on HR-QoL and disease impact to month 6 (A) mean (95% CI) change from baseline (B) by achievement of cDAPSA remission/LDA or VLDA/MDA*. *Yes/no represents achievement of cDAPSA remission/LDA and VLDA/MDA at 6 months. For PsAID-12, lower scores represent lower impact of psoriatic arthritis, with a minimal important difference for the PsAID-12 of −3.0 points.[46] cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; EQ5D, EuroQol 5-Dimension Questionnaire; HR-QoL, health-related quality of life; LDA, low disease activity; MDA, minimal disease activity; PsAID-12, 12-Item Psoriatic Arthritis Impact of Disease Questionnaire; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab; VAS, visual analogue scale; VLDA, very low disease activity.

ustekinumab-treated patients compared with TNFi, raises the possibility of confounding by indication. Moreover, TNFi drugs were grouped, whereas there may be differences in efficacy between different class members, although to our knowledge this has not been definitively demonstrated.[45] The use of etanercept in 32% of our patients could still pose questions relating to effectiveness on skin outcomes. However, this represents clinical practice and among others, the Murray *et al* study demonstrates no difference in effectiveness or persistence in PsA for etanercept vs adalimumab.[42] Other biologic modes of action, such as IL-17 inhibitors, were not available when PsABio was planned, and were not included. However, two trials comparing IL-17 inhibitors with a TNF blocker have since been published; these failed to show superiority of IL-17 blockade over TNF inhibition (or vice versa) regarding American College of Rheumatology criteria response rates, further substantiating the current study.[13 14] Thus, data from PsABio provide new insights regarding important open research questions on patients with PsA selected for biologic

treatment in routine care. No similar large-scale, real-world data comparing different biologics exist.

In conclusion, after 6 months of treatment in a routine care setting, ustekinumab and TNFi, when used as a first-line, second-line or third-line bDMARD, demonstrated a significant DAPSA score improvement from baseline, with similar achievement of MDA, cDAPSA-LDA or cDAPSA remission in patients with PsA. This translated into a considerable enhancement of health-related quality of life, and a major reduction of disease impact on daily functioning, independently of ustekinumab or TNFi use. Both baseline high disease activity and severe impact of the disease were modifiable negative predictive factors which might support early effective intervention in patients with PsA. Publication of later follow-up data will further evaluate a longer-term comparison of ustekinumab with TNFi.

Author affiliations
[1]Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria
[2]Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow, UK
[3]Department of Spondyloarthritis and Psoriatic Arthritis, VA Nasonova Research Institute of Rheumatology, Moscow, Russian Federation
[4]Division of Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center IRCCS and Humanitas University, Milan, Italy
[5]Biostatistics, Janssen-Cilag B.V, Breda, The Netherlands
[6]Division of Rheumatology, Fondazione Policlinico A Gemelli-IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy
[7]Rheumatology Department, University Hospital 12 de Octubre, Madrid, Spain
[8]Rheumatology Clinic, Naval Hospital of Athens, Athens, Greece
[9]Medical Affairs, Janssen Pharmaceuticals NV, Beerse, Belgium
[10]Department of Rheumatology, Amsterdam Rheumatology and Immunology Center, Reade & VU University Medical Center, Amsterdam, The Netherlands
[11]Service de Rhumatologie, Centre Viggo Petersen Hôpital Lariboisière, Paris, Île-de-France, France
[12]INSERM UMR-S 1132 Bioscar, Universite Paris Diderot UFR de Médecine, Paris, Île-de-France, France
[13]First Department of Propaedeutic and Internal Medicine, National and Kapodistrian University of Athens Medical School, Athens, Greece
[14]Department of Rheumatology, Universitaire Ziekenhuizen Leuven, Leuven, Belgium
[15]Skeletal Biology and Engineering Research Center, Department of Development and Regeneration, KU Leuven, Leuven, Belgium
[16]Medical Affairs, Janssen-Cilag AB, Solna, Sweden
[17]INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Sorbonne Université, Paris, France
[18]APHP, Department of Rheumatology, L'Hôpital Universitaire Pitié-Salpêtrière, Paris, France

Twitter Stefan Siebert @StefanSiebert1

Acknowledgements We thank the investigators of all study sites – the primary investigators by study countries were: Marc Vanden Berghe, Johan Vanhoof, Kurt de Vlam, Jiangang Qu, Marie-Joëlle Kaiser, Silvana Di Romana, Jan Lenaerts (Belgium); Caroline Guillibert, Roland Chapurlat, Pascal Claudepierre, Bernard Combe, Arnaud Constantin, Philippe Goupille, Pascal Hilliquin, Frédéric Lioté, Christophe Richez, Jeremie Sellam, Eric Toussirot, Laure Gossec, René-Marc Flipo, Fabienne Coury-Lucas (France); Panagiotis Athanassiou, Dimitrios Boumpas; Alexandros Garyfallos, Panagiotis Georgiou, Athanasios Georgountzos, Dimitrios Kasimos, Gkikas Katsifis, Lazaros Sakkas, Petros Sfikakis, Prodromos Sidiropoulos, Panagiotis Vlahogiannopoulos, Dimitrios Vasilopoulos (Greece); Elisa Gremese, Rosario Foti, Enrico Fusaro, Luca Idolazzi, Giovanni Lapadula, Florenzo Iannone, Marco Matucci Cerinic, Marta Mosca, Paolo Moscato, Roberto Perricone, Piercarlo Sarzi-Puttini, Carlo Francesco Selmi, Giuliana Guggino, Gabriele Valentini, Francesco Ciccia, Guido Valesini, Fabrizio Conti, Giovanna Cuomo (Italy); Marc Bijl, Eduard Griep, Marc Kok, Michael Nurmohamed, Timothy Radstake, E.F.A. Leijten, Mihaela Gamala (Netherlands); Irina Kushnir, Elena Ilivanova, Tatiana Korotaeva, Ruzana Samigullina, Natalia Sanina, Olga Uhanova, Karine Lytkina, Galina Lukina, Larisa Balykova, Elvira Otteva (Russian Federation); Beatriz Joven-Ibáñez, Ana Laiz, Jesús Rodríguez, Maria Consuelo Diaz-Miguel Perez, Eugenio Chamizo Carmona, Juan Cañete Crespillo, Joaquin Maria Belzunegui Otano, Maria García Vivar, Jaime Calvo Alén, Julio Medina Luezas, José Rodríguez Heredia, Enrique Raya Álvarez (Spain); Lisa Dunkley, Easwaradhas Gladston Chelliah, Hector Chinoy, Stephen Kelly, Deepak Jadon, Tom Sheeran, Stefan Siebert, Ellie Korendowych, Eleri Thomas, Jonathan Packham, Jonathan Marks, Pauline Ho, Antoni T Y Chan (United Kingdom). Under the direction of the authors, Cello Health MedErgy drafted the initial version of the manuscript and provided medical writing support throughout its development. The authors acknowledge Frédéric Lavie MD, PhD for his contribution in initiating the concept of the study.

Contributors JSS, SS, TVK, CS, PB, EG, BJI, GK, WN, MTN, PPS, KdV, ET and LG contributed to conceiving the study; SS, TVK, PB, EG, BEJ, WN, PPS, KdV, ET and LG contributed to the development of the study design of methodology; SS, TVK, CS, EG, BJI, GK, WN, MTN, PR, PPS, KdV, ET and LG conducted the research; JSS, SS, TVK, CS, EG, BJI, WN, MTN, PR, PPS, ET and LG planned, directed and coordinated research activity; PB, GK, PR, WN, PPS, KdV and ET contributed to formal data analysis and validation of results; JSS, SS, TVK, CS, PB, EG, BJI, GK, WN, MTN, PR, PPS, KdV, ET, LG contributed to preparing and writing the manuscript. All authors reviewed and approved the final version of the manuscript.

Funding This study was sponsored by Janssen. Medical writing and editorial support were funded by Janssen.

Disclaimer The study sponsor was involved in the study design; the collection, analysis, and interpretation of data; report writing, and preparation, review, and approval of the manuscript; and the decision to submit the manuscript for publication under the guidance of an advisory committee consisting of the authors of this manuscript. All authors 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.

Competing interests JSS reports grant/research support from: AbbVie, AstraZeneca, Eli Lilly, Roche and Novartis, and personal fees from: AbbVie, Amgen, AstraZeneca, Astro, Bristol-Myers Squibb, Celgene, Celltrion, Chugai, Eli Lilly, Gilead, ILTOO, Janssen, MSD, Novartis, Sandoz, Pfizer, Roche, Samsung, Sanofi and USB. SS reports grant/research support from: AbbVie, Boehringer Ingelheim, Celgene, GSK, Janssen, Novartis, Pfizer and UCB, and personal fees from: AbbVie, BIOCAD, Boehringer Ingelheim, Janssen, Novartis, Pfizer and UCB. TVK reports grant/research support from: Pfizer, and personal fees from: AbbVie, Amgen, BIOCAD, Celgene, Eli Lilly, Janssen, MSD, Novartis, Novartis-Sandoz, Pfizer and UCB. CS reports grant/research support from: AbbVie, Amgen, Janssen and Pfizer, and personal fees from: AbbVie, Alfa-Wassermann, Biogen Celgene, Eli Lilly, Gilead, Janssen, MSD, Novartis, Sanofi-Genzyme and Pfizer. PB reports share ownership in Johnson & Johnson, and is a full-time employee of Janssen. KdV reports grant/research support from: Celgene, and personal fees from: AbbVie, Amgen, Eli Lilly, Galapagos, Johnson & Johnson, Novartis and UCB. EG reports personal fees from: AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, MSD, Novartis, Sanofi, UCB, Roche and Pfizer. BJI reports personal fees from: AbbVie, Celgene, Janssen, MSD, Novartis and Pfizer. GK reports personal fees from: AbbVie, Aenorasis, Genesis Pharma, Janssen, MSD, Novartis, Pfizer, Roche and UCB. WN is a full-time employee of Janssen. MTN reports grant/research support from: AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Gilead/Galapagos, Janssen, Menarini, MSD, Mundipharma, Pfizer, Roche, Sanofi and UCB, and personal fees from: AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Gilead/Galapagos, Janssen, Menarini, MSD, Mundipharma, Pfizer, Roche, Sanofi and UCB. PR reports personal fees from: AbbVie, Celgene, Janssen, MSD, Novartis, Pfizer and UCB. PPS has no conflicts of interest to report. ET is a full-time employee of Janssen. LG reports grant/research support from: Amgen, Galapagos, Janssen, Eli Lilly, Pfizer, Sanofi-Aventis and Sandoz, and personal fees from: AbbVie, Amgen, Biogen, Bristol-Myers Squibb, Celgene, Eli Lilly, Galapagos, Gilead, Janssen, Novartis, Pfizer, Samsung-Bioepis, Sandoz, Sanofi-Aventis and UCB.

Patient consent for publication Not required.

Ethics approval This study complied with ethics requirements as specified by the Independent Ethics Committee/Institutional Review Board and by local regulations. Each participant signed a participation agreement/informed consent form in line with local regulations and trial sponsor policy, before data collection.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Access to anonymised individual participant-level data will not be provided for this trial as it meets one or more of the exceptions described on https://yoda.yale.edu/ under 'Data Use Agreement-Janssen Pharmaceuticals DUA'.

ORCID iDs
Josef S Smolen http://orcid.org/0000-0002-4302-8877
Carlo Selmi http://orcid.org/0000-0002-0323-0376
Pascal Richette http://orcid.org/0000-0003-2132-4074
Petros P Sfikakis http://orcid.org/0000-0001-5484-2930
Laure Gossec http://orcid.org/0000-0002-4528-310X

REFERENCES

1 Van den Bosch F, Coates L. Clinical management of psoriatic arthritis. *Lancet* 2018;391:2285–94.
2 Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. *Lancet* 2018;391:2273–84.
3 Kerschbaumer A, Smolen JS, Dougados M, *et al*. Pharmacological treatment of psoriatic arthritis: a systematic literature research for the 2019 update of the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis* 2020;79:778–86.
4 Gossec L, Baraliakos X, Kerschbaumer A, *et al*. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* 2020;79:700.1–12.
5 Queiro R, Coto-Segura P. Ustekinumab in psoriatic arthritis: need for studies from real-world evidence. *Expert Opin Biol Ther* 2018;18:931–5.
6 Thibodaux RJ, Triche MW, Espinoza LR. Ustekinumab for the treatment of psoriasis and psoriatic arthritis: a drug evaluation and literature review. *Expert Opin Biol Ther* 2018;18:821–7.
7 Cafaro G, McInnes IB. Psoriatic arthritis: tissue-directed inflammation? *Clin Rheumatol* 2018;37:859–68.
8 Sakkas LI, Zafiriou E, Bogdanos DP. Mini review: new treatments in psoriatic arthritis. Focus on the IL-23/17 axis. *Front Pharmacol* 2019;10:872.
9 Davari P, Leo MS, Kamangar F, *et al*. Ustekinumab for the treatment of psoriatic arthritis: an update. *Clin Cosmet Investig Dermatol* 2014;7:243–9.
10 McInnes IB, Kavanaugh A, Gottlieb AB, *et al*. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* 2013;382:780–9.
11 Ritchlin C, Rahman P, Kavanaugh A, *et al*. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis* 2014;73:990–9.
12 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.
13 McInnes IB, Behrens F, Mease PJ, *et al*. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. *Lancet* 2020;395:1496–505.
14 Mease PJ, Smolen JS, Behrens F, *et al*. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. *Ann Rheum Dis* 2020;79:123–31.
15 Vandendorpe A-S, de Vlam K, Lories R. Evolution of psoriatic arthritis study patient population characteristics in the era of biological treatments. *RMD Open* 2019;5:e000779.
16 Gossec L, McGonagle D, Korotaeva T, *et al*. Minimal disease activity as a treatment target in psoriatic arthritis: a review of the literature. *J Rheumatol* 2018;45:6–13.
17 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.
18 Tucker LJ, Ye W, Coates LC. Novel concepts in psoriatic arthritis management: can we treat to target? *Curr Rheumatol Rep* 2018;20:71.
19 Taylor W, Gladman D, Helliwell P, *et al*. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665–73.
20 Aletaha D, Alasti F, Smolen JS. Disease activity states of the DAPSA, a psoriatic arthritis specific instrument, are valid against functional status and structural progression. *Ann Rheum Dis* 2017;76:418–21.
21 Coates LC, Helliwell PS. Defining low disease activity states in psoriatic arthritis using novel composite disease instruments. *J Rheumatol* 2016;43:371–5.
22 Healy PJ, Helliwell PS. Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. *Arthritis Rheum* 2008;59:686–91.
23 Harrington D, D'Agostino RB, Gatsonis C, *et al*. New Guidelines for Statistical Reporting in the *Journal*. *N Engl J Med Overseas Ed* 2019;381:285–6.
24 Moll JM, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973;3:55–78.
25 Eder L, Chandran V, Schentag CT, *et al*. Time and predictors of response to tumour necrosis factor-alpha blockers in psoriatic arthritis: an analysis of a longitudinal observational cohort. *Rheumatology* 2010;49:1361–6.
26 Glintborg B, Østergaard M, Dreyer L, *et al*. Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor α therapy: results from the nationwide Danish DANBIO registry. *Arthritis Rheum* 2011;63:382–90.
27 Batalla A, González-Fernández D, González-Lara L, *et al*. Cardiovascular risk factors influence response to biological therapies in psoriasis. *J Am Acad Dermatol* 2015;73:327–9.
28 Lupoli R, Pizzicato P, Scalera A, *et al*. Impact of body weight on the achievement of minimal disease activity in patients with rheumatic diseases: a systematic review and meta-analysis. *Arthritis Res Ther* 2016;18:297.
29 Ogdie A, Palmer JL, Greenberg J, *et al*. Predictors of achieving remission among patients with psoriatic arthritis initiating a tumor necrosis factor inhibitor. *J Rheumatol* 2019;46:475–82.
30 Lubrano E, Perrotta FM, Scriffignano S, *et al*. Sustained very low disease activity and remission in psoriatic arthritis patients. *Rheumatol Ther* 2019;6:521–8.
31 Napolitano M, Costa L, Caso F, *et al*. Minimal disease activity in patients with psoriatic arthritis treated with ustekinumab: results from a 24-week real-world study. *Clin Rheumatol* 2017;36:1589–93.
32 Queiro R, Brandy A, Rosado MC, *et al*. Minimal disease activity and patient-acceptable symptom state in psoriatic arthritis: a real-world evidence study with ustekinumab. *J Clin Rheumatol* 2018;24:381–4.
33 Almirall M, Rodriguez J, Mateo L, *et al*. Treatment with ustekinumab in a Spanish cohort of patients with psoriasis and psoriatic arthritis in daily clinical practice. *Clin Rheumatol* 2017;36:439–43.
34 Chimenti MS, Ortolan A, Lorenzin M, *et al*. Effectiveness and safety of ustekinumab in naïve or TNF-inhibitors failure psoriatic arthritis patients: a 24-month prospective multicentric study. *Clin Rheumatol* 2018;37:397–405.
35 Iannone F, Santo L, Bucci R, *et al*. Drug survival and effectiveness of ustekinumab in patients with psoriatic arthritis. Real-life data from the biologic Apulian registry (BIOPURE). *Clin Rheumatol* 2018;37:667–75.
36 Mease P, van der Heijde D, Landewé R, *et al*. Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. *Ann Rheum Dis* 2018;77:890–7.
37 Kavanaugh A, Husni ME, Harrison DD, *et al*. Safety and efficacy of intravenous golimumab in patients with active psoriatic arthritis: results through week twenty-four of the GO-VIBRANT study. *Arthritis Rheumatol* 2017;69:2151–61.
38 Mease PJ, Fleischmann R, Deodhar AA, *et al*. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014;73:48–55.
39 Mease PJ, Gottlieb AB, van der Heijde D, *et al*. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. *Ann Rheum Dis* 2017;76:1550–8.
40 Smolen JS, Schöls M, Braun J, *et al*. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force [correction appears in *Ann Rheum Dis* 2018;77:472]. *Ann Rheum Dis* 2018;77:3–17.
41 van Mens LJJ, de Jong HM, Fluri I, *et al*. Achieving remission in psoriatic arthritis by early initiation of TNF inhibition: a double-blind, randomised, placebo-controlled trial of golimumab plus methotrexate versus placebo plus methotrexate. *Ann Rheum Dis* 2019;78:610–6.
42 Murray K, Turk M, Alammari Y, *et al*. Long-term remission and biologic persistence rates: 12-year real-world data. *Arthritis Res Ther* 2021;23:25.
43 Hammer GP, du Prel J-B, Blettner M. Avoiding bias in observational studies: part 8 in a series of articles on evaluation of scientific publications. *Dtsch Arztebl Int* 2009;106:664–8.
44 Sjoding MW, Luo K, Miller MA, *et al*. When do confounding by indication and inadequate risk adjustment bias critical care studies? A simulation study. *Crit Care* 2015;19:195.
45 Smolen JS, Burmester G-R, Combe B, *et al*. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. *Lancet* 2016;388:2763–74.
46 Holland R, Tillett W, Korendowych E, *et al*. Validation of the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire and its potential as a single-item outcome measure in clinical practice. *Ann Rheum Dis* 2018;77:343–7.

CLINICAL SCIENCE

Targeted metabolomic profiling and prediction of cardiovascular events: a prospective study of patients with psoriatic arthritis and psoriasis

Keith Colaco,[1,2,3] Ker-Ai Lee,[4] Shadi Akhtari,[5,6] Raz Winer,[7] Paul Welsh,[8] Naveed Sattar,[8] Iain B McInnes,[9] Vinod Chandran,[3,6] Paula Harvey,[5,6] Richard J Cook,[4] Dafna D Gladman ,[3,6] Vincent Piguet,[1,6] Lihi Eder [1,6]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220168).

For numbered affiliations see end of article.

Correspondence to
Dr Lihi Eder, Women's College Research Institute, Women's College Hospital, Toronto, Canada;
Lihi.EDER@wchospital.ca

This study reports work that was previously presented at the 2020 American College of Rheumatology Annual Meeting: Colaco K, Lee K, Akhtari S, *et al*. Targeted Metabolomic Profiling and Prediction of Cardiovascular Events: A Prospective Study of Patients with Psoriatic Arthritis and Psoriasis [(abstract]). Arthritis Rheumatol. 2020; 72 (suppl 10).

Received 15 February 2021
Accepted 19 May 2021
Published Online First 28 May 2021

To cite: Colaco K, Lee K-A, Akhtari S, *et al*. *Ann Rheum Dis* 2021;**80**:1429–1435.

ABSTRACT

Objective In patients with psoriatic disease (PsD), we sought serum metabolites associated with cardiovascular (CV) events and investigated whether they could improve CV risk prediction beyond traditional risk factors and the Framingham Risk Score (FRS).

Methods Nuclear magnetic resonance metabolomics identified biomarkers for incident CV events in patients with PsD. The association of each metabolite with incident CV events was analysed using Cox proportional hazards regression models first adjusted for age and sex, and subsequently for traditional CV risk factors. Variable selection was performed using penalisation with boosting after adjusting for age and sex, and the FRS.

Results Among 977 patients with PsD, 70 patients had incident CV events. In Cox regression models adjusted for CV risk factors, alanine, tyrosine, degree of unsaturation of fatty acids and high-density lipoprotein particles were associated with decreased CV risk. Glycoprotein acetyls, apolipoprotein B and cholesterol remnants were associated with increased CV risk. The age-adjusted and sex-adjusted expanded model with 13 metabolites significantly improved prediction of CV events beyond the model with age and sex alone, with an area under the receiver operator characteristic curve (AUC) of 79.9 versus 72.6, respectively (p=0.02). Compared with the FRS alone (AUC=73.9), the FRS-adjusted expanded model with 11 metabolites (AUC=75.0, p=0.72) did not improve CV risk discrimination.

Conclusions We identify novel metabolites associated with the development of CV events in patients with PsD. Further study of their underlying causal role may clarify important pathways leading to CV events in this population.

Key messages

What is already known about this subject?

- Lack of effective biomarkers for cardiovascular (CV) risk prediction in patients with psoriatic disease (PsD) delays early intervention and prompt treatment.

What does this study add?

- A range of novel metabolites in biochemical pathways associated with higher CV risk, but not routinely measured in clinical practice, are identified, offering novel insights into the metabolic nature of atherosclerosis and PsD.
- A combined model that included 13 metabolite biomarkers in addition to age and sex demonstrated good performance in predicting CV risk in patients with PsD.

How might this impact on clinical practice or future developments?

- This study suggests potential biomarkers that may offer early mechanistic clues leading to CV events, and may aid in risk stratification of patients with PsD in the future.

INTRODUCTION

Psoriasis and psoriatic arthritis, collectively referred to as psoriatic disease (PsD), are chronic immune-mediated diseases primarily affecting the skin and joints. PsD is associated with an increased risk of cardiometabolic diseases, which is partially independent of traditional cardiovascular (CV) risk factors.[1 2] PsD is also associated with systemic inflammation that is not limited to the skin or musculoskeletal structures. It is now considered that atherosclerosis is a chronic inflammatory disease whereby interactions between immune mechanisms and plasma lipid particles trigger the formation of atherosclerotic plaques in the vascular wall.[3] In patients with PsD, metabolic abnormalities and dysregulated serum levels of pro-inflammatory cytokines drive the atherosclerotic process, leading to the development of clinical CV events.[4 5] Taken together, there is compelling evidence that PsD and atherosclerotic pathology share common inflammatory origins.[6]

The Framingham Risk Score (FRS) is widely used in North America to assess the 10-year CV risk by incorporating traditional CV risk factors.[7] However, the use of the FRS and other established clinical prediction algorithms to predict CV risk in PsD and other inflammatory rheumatic diseases tend to underestimate the true CV risk since they do not accurately reflect the heightened activity of inflammatory pathways which contributes to CV risk in patients with PsD.[8 9] The consequences of underestimating CV risk in the PsD population in clinical practice may result in a missed opportunity to intervene early.[10]

Metabolomics elucidates circulating metabolites across multiple biological pathways, providing a comprehensive snapshot of metabolic state. High-throughput nuclear magnetic resonance (NMR) spectroscopy enables metabolite profiling of epidemiological cohorts, thereby advancing our understanding of atherosclerotic disease pathogenesis and potentially improving risk prediction by incorporating information from novel biomarkers in addition to traditional CV risk factors. Few large-scale applications of serum NMR metabolomics in the general population have been used to identify biomarkers for disease events and risk prediction. Such studies identified significant associations of various metabolites with CV disease,[11–13] all-cause mortality,[14] inflammation[15] and type 2 diabetes.[16–18]

Investigations of the psoriatic blood metabolome revealed differences in metabolite profiles compared with healthy individuals.[19] These included metabolite changes that may reflect local inflammatory milieu, and elevations of certain plasma amino acids that have been implicated in obesity, diabetes and CV disease.[20 21] While many of these mechanistic studies used untargeted metabolomics in small samples to uncover new metabolites linked to PsD, no studies investigated the relationship between metabolites and CV events in a large cohort of patients with PsD. Given the metabolic associations identified with atherosclerosis, PsD may serve as a useful condition to investigate the interaction between inflammation, metabolic abnormalities and atherosclerosis, offering the potential to identify new CV disease biomarkers and improve our understanding of pathways that drive the increased CV risk.

In this study, we aimed to identify serum metabolites associated with risk of developing CV events in patients with PsD, and which therefore may be of interest in terms of aetiology. We then aimed to determine whether metabolites could be useful in CV risk prediction beyond traditional risk factors and the FRS.

METHODS

Study population

We assessed the association between a targeted panel of metabolites and incident CV events in the University of Toronto PsD cohort, described in online supplemental. Annual serum samples have been collected and stored in a biobank since 2002, thus patients entered the study at the date they provided their first serum sample. Inclusion criteria included having a serum sample in the biobank, no history of CV events at study entry, and being followed for at least 1 year following study entry.

Framingham Risk Score

The FRS was calculated for each patient to estimate the 10-year risk of fatal and non-fatal CV disease.[22] The risk factors included in the score were age, sex, current smoking, systolic blood pressure, treatment for hypertension, diabetes, total cholesterol and high-density lipoprotein (HDL) cholesterol.

Metabolite quantification

A targeted, high-throughput NMR metabolomics platform was used to quantify 68 lipid and metabolite measures from the first available serum sample. The NMR-based profiling, performed by Nightingale Health, has previously been used in various epidemiological studies, and details of the experimental protocol have been described.[23 24] All metabolites were measured in a single experimental setup that allows for simultaneous quantification of routine lipids, total lipid concentrations of lipoprotein subclasses, fatty acid composition, various glycolysis precursors, ketone bodies and amino acids in absolute concentration units (online supplemental table 1). This platform includes both known metabolic risk factors and metabolites from multiple physiological pathways that have been previously examined in relation to fatal and non-fatal CV disease in large population-based studies.[25] Pyruvate, lactate, glycerol, acetate and glutamine were excluded from analyses as a result of quality control measures that identified issues with sample integrity and biomarker quantification.

Case definition of CV outcomes

A composite endpoint was defined as the occurrence of the first clinical CV event. Within 10 years of biomarker measurement, the following CV events were identified: angina pectoris, myocardial infarction, transient ischaemic attack (TIA), ischaemic cerebrovascular accident (CVA), heart failure, revascularisation procedures and CV death. Revascularisation procedures included coronary angioplasty, coronary bypass surgery, carotid endarterectomy and vascular surgery for peripheral artery disease. Procedures for identifying and verifying CV outcomes are described in online supplemental.

Statistical analyses

Baseline characteristics were calculated as the mean and SD for continuous variables, or frequency for categorical variables. Values for metabolites below the limit of detection, which comprised less than 0.5% of metabolites profiled, were substituted with the lowest value for the metabolite. All metabolite concentrations were log-transformed to better approximate the normal distribution, and standardised to make them directly comparable. The statistical analysis was performed in two stages. The first stage aimed to identify individual metabolites associated with high CV risk in order to elucidate underlying mechanisms of CV disease in PsD. Associations with incident CV events were analysed separately for each metabolite using a series of Cox proportional hazards regression models, which involved the cause-specific hazard for the event of interest, treating death due to non-CV causes as the competing event. Individuals entered the risk set at the date of the first available (baseline) serum sample and the event occurred at the date of the first CV event within 10 years of acquiring the baseline serum sample. Patients who were event-free at the date they were last known to be alive, had their follow-up censored at this time. Metabolite associations were first adjusted for age and sex, followed by traditional non-laboratory CV risk factors including age, sex, smoking status, diabetes mellitus, hypertension and body mass index. HRs and 95% CIs of each metabolite were reported.

Subsequently, we assessed the ability of all metabolites to predict the composite CV endpoint. Variable selection was performed using a penalisation and boosting algorithm.[26 27] Boosting is an ensemble-type method for building predictive models which is well-suited to settings where important covariates are sparse among a larger set of potential predictors. The boosting algorithm employed fivefold cross-validation to select the tuning parameter for the penalised regression and to determine the number of boosting steps. Two proportional sub-distribution hazards (Fine-Gray) regression models were considered, with non-CV death considered as a competing event[28–30]: (i) the first base model adjusted only for age and sex, and (ii) the second base model adjusted for the FRS. All metabolites were then added to the respective base model, to create expanded models. The predictive ability of the base model (without metabolites) and the expanded model (with

Table 1 Baseline characteristics of the study population

Variable	All participants (N=977)	Participants without CV events (n=907)	Participants with CV events (n=70)
	Mean±SD/frequency (%)		
PsA	639 (65.4%)	582 (64.2%)	57 (81.4%)
Psoriasis without arthritis	338 (34.6%)	325 (35.8%)	13 (18.6%)
Age, years	49±12.6	48±12.4	60±9.8
Sex: male	536 (54.9%)	494 (54.5%)	42 (60%)
Ethnicity: Caucasian	817 (83.7%)	753 (83.1%)	64 (91.4%)
Duration of PsA, years	12±10.3	11±10.1	17±11.8
Duration of Psoriasis, years	20±14.1	20±14.0	23±15.4
Smoking status			
Never smoker	521 (53.3%)	492 (54.2%)	29 (41.4%)
Past smoker	301 (30.8%)	270 (29.8%))	31 (44.3%)
Current smoker	155 (15.9%)	145 (16%)	10 (14.3%)
PASI	4.1±6.2	4.1±6.2	4.1±5.9
Swollen joint count*	1.5±3.3	1.6±3.4	0.9±2.5
Tender joint count*	3.8±7.3	3.8±7.4	2.7±5.6
HAQ	0.37±0.5	0.36±0.5	0.54±0.6
Current use of NSAIDs (daily use)	260 (26.6%)	236 (26%)	24 (34.3%)
Current use of DMARD	352 (36%)	318 (35.1%)	34 (48.6%)
Current use of biologicals	207 (21.2%)	193 (21.3%)	14 (20%)
Total cholesterol, mmol/L	4.2±0.9	4.2±0.9	4.4±0.9
LDL cholesterol, mmol/L	1.6±0.5	1.6±0.5	1.7±0.5
HDL cholesterol, mmol/L	1.2±0.3	1.2±0.3	1.2±0.3
Body mass index, kg/m^2	28.7±5.9	28.5±5.9	30.9±6.5
Diabetes mellitus	71 (7.3%)	61 (6.7%)	10 (14.3%)
Hypertension†	266 (27.2%)	222 (24.5%)	44 (62.9%)
Use of anti-hypertensive medication	200 (20.5%)	165 (18.2%)	35 (50%)
Use of lipid-lowering medication	99 (10.1%)	81 (8.9%)	18 (25.7%)
Framingham Risk Score	8.1±8.5	7.4±7.8	17.3±10.9

Medians (25th to 75th percentile) are provided for continuous variables in online supplemental table 2.
*Assessed only for PsA patients.
†Systolic blood pressure >140 mm Hg or use of anti-hypertensive medications.
DMARD, disease-modifying anti-rheumatic drug; HAQ, Health Assessment Questionnaire; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NSAIDs, non-steroidal anti-inflammatory drugs; PASI, psoriasis area and severity index; PsA, psoriatic arthritis.

selected metabolites) was assessed using the area under the receiver operator characteristic curve (AUC).[31] Analyses were performed with R (V.3.6.2) and SAS Studio V.3.8.

Patient and public involvement

This study was conducted without patient and public involvement.

RESULTS

From 2002 to 2019, a total of 977 participants (639 with PsA, 338 with cutaneous psoriasis only) were evaluated. During a mean follow-up of 7.1 years (6894 person-years), 70 patients developed an incident CV event (9 angina; 19 myocardial infarction; 10 heart failure; 6 TIA; 10 CVA; 11 revascularisation; 5 CV death). Baseline characteristics of the study population are shown in table 1.

Association between individual metabolites and CV events

To elucidate the link between PsD and CV disease and generate hypotheses on the roles of relevant serum metabolites, we examined each metabolite's association with incident CV events. The association of candidate biomarkers with incident CV events are shown in figure 1.

In the age-adjusted and sex-adjusted models, 32 metabolites were significantly associated with incident CV events. Notable associations with increased CV risk were observed for higher levels of glucose, glycoprotein acetyls (GlycA), monounsaturated fatty acids to total fatty acids ratio (MUFA%), saturated fatty acids, apolipoprotein B (ApoB), triglycerides, total very low-density lipoprotein (VLDL) cholesterol concentration, VLDL diameter, as well as VLDL particles ranging in size from very small to extremely large. Inverse associations with CV risk were found for HDL, including the total concentration and for large HDL particles, higher degree of unsaturation of fatty acids (indicated by the number of double bonds per fatty acid), as well as the ratio of the following fatty acids relative to total fatty acids: docosahexaenoic acid (an omega-3 fatty acid) (DHA%), linoleic acid (an omega-6 fatty acid) (LA%), total omega-6 fatty acids (omega-6 %) and polyunsaturated fatty acids (PUFA%).

In a model adjusted for traditional non-laboratory CV risk factors (age, sex, smoking status, diabetes mellitus, hypertension and body mass index), 13 metabolites were associated with incident CV events. GlycA, ApoB, remnant cholesterol, triglycerides in intermediate-density lipoproteins (IDLs) and low-density lipoproteins (LDLs), VLDL cholesterol and very small VLDL particles were associated with higher CV risk, while the degree of unsaturation of fatty acids, alanine, tyrosine, total HDL cholesterol and medium and large HDL particles were associated with lower CV risk.

Metabolites and CV risk prediction

A penalisation and boosting algorithm selected candidate biomarkers and constructed two predictive models for CV events. Optimal models based on fivefold cross validation included 13 metabolites (in a model adjusted for age and sex), and 11 metabolites (in a model adjusted for the FRS). The selected metabolites with corresponding regression coefficients are listed in table 2.

A diverse array of metabolites was selected in both models, including amino acids, fatty acids, lipoprotein subclasses, ketone bodies, glycolysis precursors and measures of fluid balance. The following six metabolites were included in both models: alanine, DHA, degree of unsaturation of fatty acids, triglycerides in IDL cholesterol, glucose, and acetoacetate.

To assess the potential of metabolite biomarkers to improve CV risk discrimination, the predictive accuracy of a base model (without metabolites) was compared with an expanded model (with the selected metabolites). The age-adjusted and sex-adjusted expanded model with metabolites significantly improved risk prediction accuracy compared with the base model that included age and sex alone (AUC 79.9 (95% CI 72.4 to 87.5) vs 72.6 (95% CI 65.4 to 79.7), p=0.02) (figure 2A). However, the performance of the FRS-adjusted expanded model with metabolites was not significantly different than the base model that included only the FRS (AUC 75 (95% CI 66 to 83.9) vs 73.9 (95% CI 66.4 to 81.4), p=0.72) (figure 2B).

DISCUSSION

Using a targeted NMR-based metabolomics platform in patients with PsD, we identified a range of metabolites in biochemical pathways that were associated with higher CV risk. Most of

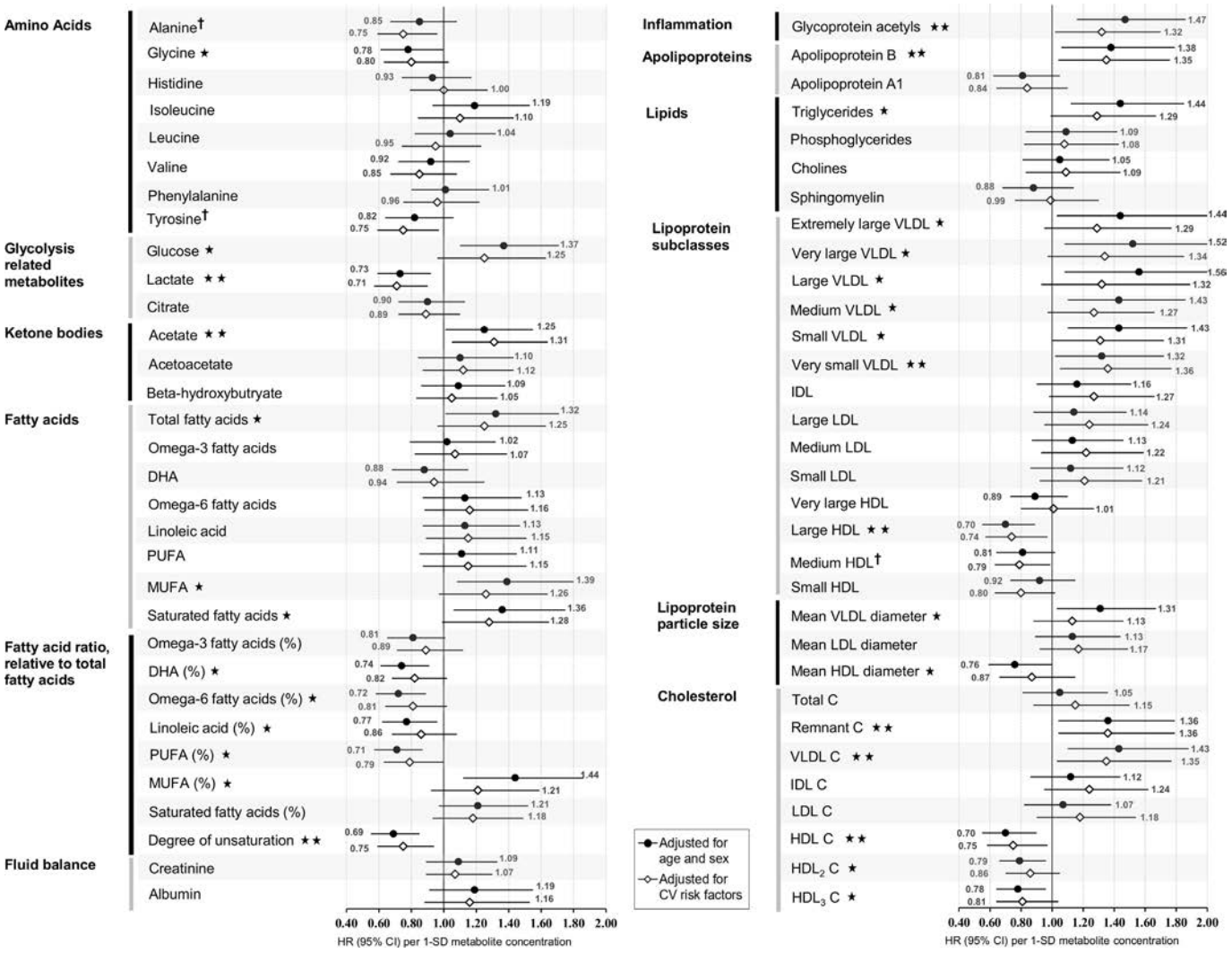


Figure 1 The association between individual metabolites and incident CV events in patients with psoriatic disease by Cox proportional hazards models (n=977, 70 incident events). Sixty-eight metabolite measures were individually analysed in a multivariate Cox model adjusted for age and sex, as well as traditional non-laboratory CV risk factors: smoking, diabetes, hypertension, body mass index. HRs are for standardised log-transformed metabolite concentration. Error bars denote 95% CIs. *P<0.05 (in age-adjusted and sex-adjusted model only). **P<0.05 (in both models adjusted for age and sex, and CV risk factors). †P<0.05 (in model adjusted for CV risk factors only). C, cholesterol; CV, cardiovascular; DHA, docosahexaenoic acid; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; VLDL, very low-density lipoprotein.

these metabolites, which are not routinely measured in clinical practice, offer novel insights into the metabolic nature of atherosclerosis and PsD. We highlight findings of ApoB and GlycA, which extend and validate other work, as well as potential underlying mechanisms of amino acids (phenylalanine, tyrosine, alanine) and DHA and their links to obesity, diabetes and renal impairment, which are common among patients with PsD. Some of these biomarkers were selected in a combined model that included 13 metabolites in addition to age and sex—this model demonstrated good performance in predicting CV risk. We do not advocate that NMR metabolomics should replace traditional risk factors in CV risk prediction on the basis of our result alone. Rather, these data allude to metabolomics identifying potentially important risk factors for CV risk prediction, but also to pathways requiring additional research to understanding potential causal mechanisms in PsD.

Elevations of conventional lipid and cholesterol particles, such as triglycerides, LDL and HDL cholesterol, and their associations with CV risk are consistent with current understanding of CV disease and reflected in clinical guidelines for use of lipid-lowering therapy. Large HDL particles and VLDL particle diameter were significantly associated with lower and higher CV risk, respectively. Although lipoprotein subclasses are highly correlated with routine lipid measures, certain subclasses, such as particle size, have been reported to augment risk prediction of subclinical atherosclerosis and may reflect the underlying biology of atherosclerosis.[32 33] Remnant cholesterol (which comprise the cholesterol content of all triglyceride-rich lipoproteins, such as IDL and VLDL particles) and ApoB were associated with a 30%–40% higher risk of CV events per SD increase. The association of cholesterol remnants with CV events confirm their suspected role in atherogenesis as an additional cause of CV disease and all-cause mortality.[34–36] ApoB, a primary constituent of LDL and triglyceride-rich lipoproteins and their remnants, is considered to be a direct measure of the total number of circulating atherogenic lipoproteins. Several studies demonstrated that plasma levels of ApoB predict risk of ischaemic CV disease in the general population, although its incremental value above

Table 2 Regression coefficients of the selected metabolites models adjusted for age and sex, and the FRS

Category	Metabolite	Model adjusted for age and sex	Model adjusted for the FRS
Amino Acids	Alanine	−0.1179	−0.1720
	Glycine	−0.0339	
	Phenylalanine		+0.0085
	Tyrosine	−0.1010	
Fatty acid ratios, relative to total fatty acids	Linoleic acid		−0.0940
	Docosahexaenoic acid	−0.0862	−0.0874
	Polyunsaturated fatty acids		−0.0137
	Degree of unsaturation of fatty acids, double bonds per fatty acid	−0.1265	−0.0173
Fluid Balance	Albumin	+0.0685	
	Creatinine		−0.0152
Glycerides	Triglycerides in IDL cholesterol	+0.1546	+0.0744
Glycolysis precursors	Glucose	+0.1391	+0.0624
Inflammation	Glycoprotein acetyls	+0.1478	
Ketone bodies	Acetoacetate	+0.0464	+0.1110
Lipoprotein subclasses	HDL_2 cholesterol		+0.0144
	HDL_3 cholesterol	−0.0211	
	Medium HDL	−0.0296	
	Large HDL	−0.0309	

FRS, Framingham Risk Score; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein.

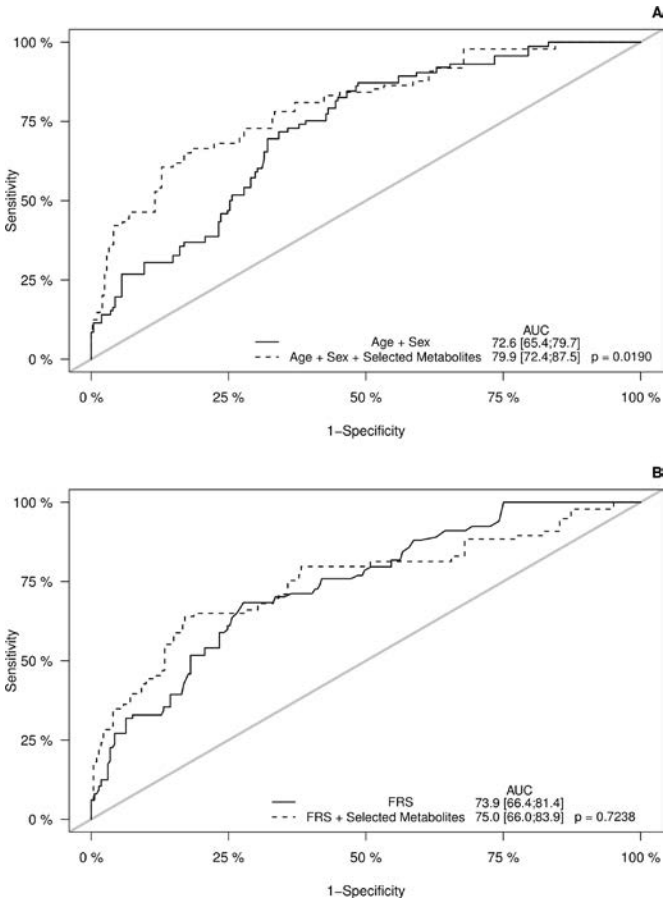


Figure 2 Comparison of the predictive performance of base models and expanded models (age and sex plus selected metabolites) for prediction of cardiovascular events. (A) Performance of a model with age and sex alone is compared with a model with age and sex plus selected metabolites. (B) Performance of the Framingham Risk Score (FRS) is compared with a model with the FRS plus selected metabolites. AUC, area under the receiver operator characteristic curve.

simple lipid measures is unclear.[37 38] That noted, recent genetic evidence suggests that the number of ApoB-carrying particles determines the actual lipid-associated CV risk.[39] Patients with PsD have an increased risk of developing dyslipidaemia,[40] and a recent meta-analysis showed that ApoB levels were significantly higher in patients with psoriasis compared with controls.[41] Therefore, it has been suggested that ApoB is more strongly associated with early atherosclerosis and the development of CV events, with potential advantages over LDL and HDL cholesterol.

GlycA, a systemic inflammatory marker that reflects the abundance of glycoproteins involved in the acute-phase response, is associated with circulating leucocytes and neutrophil activity, and concentrations of tumour necrosis factor-alpha and interleukin 6.[15 42] In the general population, GlycA has been shown to predict risk of all-cause mortality and CV disease, even when adjusting for C reactive protein.[14 43] In patients with rheumatoid arthritis, lupus and psoriasis, GlycA concentrations are higher compared with healthy individuals and correlate with measures of disease activity and subclinical CV disease.[42 44] Taken together, these data support the concept that GlycA may capture different aspects of the inflammatory response, and therefore reflects the importance of inflammation in atherosclerotic CV events in patients with PsD.

Our findings highlight the potential role of amino acids in CV disease. Concentrations of branched chain amino acids (BCAAs) (leucine, isoleucine, valine) and aromatic amino acids (phenylalanine, tyrosine) correlate with obesity and serum insulin.[45] These findings are corroborated by recent prospective metabolomic studies of the general population revealing strong associations of BCAAs (and phenylalanine and tyrosine) with obesity, insulin resistance and risk of developing diabetes.[16 23 46 47] While neither BCAAs were associated with CV events in this study, phenylalanine was positively associated with CV events in the FRS-adjusted expanded model. Tyrosine was independently associated with a lower risk of CV events after adjusting for traditional non-laboratory CV risk factors, which included body mass index and diabetes status. Indeed, impaired conversion of phenylalanine to tyrosine has been reported in renal disease,[48] and a previous study of diabetes patients reported strong correlations of tyrosine with the estimated glomerular filtration rate and urine albumin-to-creatinine ratio.[49] Therefore, given the increased risk of chronic kidney disease in psoriatic patients,[50] these amino acids may be strong surrogates of renal function,[13] in line with our data. Similar results were observed for alanine. While one study demonstrated a link between alanine and incident type 2 diabetes,[18] it is difficult to compare results owing to differences in study outcomes and populations. However, it is interesting that multiple amino acids, particularly the BCAAs, are modulators of insulin secretion and may promote diabetes via hyperaminoacidaemia.[16] Psoriasis and PsA are known to be associated with elevated risk of diabetes when accounting for obesity and lifestyle factors.[51]

We examined the ability of metabolites to improve CV risk prediction compared with conventional methods. A prediction model that included a combination of age, sex and 13 metabolites showed good performance (AUC of 80) that was superior

to the base model of age and sex alone, which raises the question whether biomarkers could be used to improve CV risk prediction in PsD. Currently, studies using this approach are sparse.[52] The addition of metabolites to the FRS did not show improvement in CV risk prediction. The lack of improvement in performance is consistent with other studies of inflammatory rheumatic diseases that attempted to add biomarkers, multipliers and disease-specific factors to the FRS and other conventional risk scores.[8] Compared with the FRS, the superior performance of the age-adjusted and sex-adjusted model in this study may be a more accurate representation of the metabolic nature of CV risk in psoriatic patients, since the disease may be driven by distinct aetiological pathways compared with the general population.

The age-adjusted and sex-adjusted model retained few metabolites, particularly DHA, found to predict incident CV events in the general population. In a large prospective study and meta-analysis of three population-based cohorts in Finland and the UK which tested the same metabolomics platform, four metabolites were associated with future CV events after adjusting for traditional CV risk factors (including routine lipids).[11] Phenylalanine and MUFA were identified as biomarkers of higher CV risk, whereas omega-6 fatty acids and DHA were biomarkers of lower CV risk. In our model, DHA had a similar direction of association along with other metabolite measures known to have protective associations, such as the degree of unsaturation of fatty acids, HDL_3 cholesterol and medium and large HDL particles. HDL particle profile and unsaturated fatty acids have been suggested for risk stratification, as they have been proposed by others to have triglyceride-lowering and anti-inflammatory effects.[53]

Our study has several strengths. This is the first study to assess CV risk prediction and investigate serum metabolites in a large longitudinal cohort of patients with PsD. Serum samples were collected during a time period when lipid-lowering therapies and disease-modifying antirheumatic drugs were widely available; thus, the benefit of modern preventive treatments is likely reflected in the reported CV risk estimates. We used a targeted NMR metabolomics platform that includes many routine clinical and epidemiological markers, resulting in quantitative data that can be meta-analysed across multiple cohorts in future studies of PsD. Some limitations should be considered. Metabolite coverage is limited by targeted approaches and NMR spectroscopy, in comparison with other analytical techniques such as mass spectrometry. Therefore, targeted metabolomics profiling may miss candidate biomarkers which might further improve risk prediction. Second, the study may have limited power in identifying significant associations due to the low number of CV events in the sample population.

Psoriasis, and particularly PsA, are heterogeneous diseases that require evaluation of multiple domains. Our findings are particularly noteworthy in the context of novel metabolites that are not part of routine clinical assessments, and may be important in driving elevations in CV risk in psoriatic patients. This investigation, the first to explore the relationship between metabolites and CV events in a large cohort of patients with PsD, highlights the potential value of extending beyond traditional CV factors to improve risk assessment at an early phase of atherosclerosis development. The identified biomarkers offer novel insights into the metabolic nature of atherosclerosis and PsD. A combination of amino acids, inflammation-related metabolites (GlycA) and both pro-inflammatory and anti-inflammatory lipid particles were associated with CV risk—these measures may offer early mechanistic clues leading to CV events, and in the future, may aid in risk stratification. Although further study is needed before recommendations can be made, the use of targeted metabolomics profiling elucidates many of the biological mechanisms underlying the associations with CV disease in patients with PsD.

Author affiliations
[1]Women's College Research Institute, Women's College Hospital, Toronto, Ontario, Canada
[2]Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[3]Schroeder Arthritis Institute, University Health Network, Toronto, Ontario, Canada
[4]Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, Ontario, Canada
[5]Department of Cardiology, Women's College Hospital, Toronto, Ontario, Canada
[6]Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[7]Department of Neurology, Rambam Health Care Campus, Haifa, Israel
[8]BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK
[9]Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK

Contributors All authors were involved in study conception and design. KC, K-AL, RJC and LE analysed and interpreted the data. All authors were involved in interpretation of the results and drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. LE had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding KC is supported by the Enid Walker Estate, Women's College Research Institute, Arthritis Society (TGP-19-0446), National Psoriasis Foundation (Early Career Grant) and the Edward Dunlop Foundation. LE is supported by a Young Investigator Award from the Arthritis Society and an Early Researcher Award from the Ontario Ministry of Science and Innovation. VC is supported by a Pfizer Chair Research Award, Rheumatology, University of Toronto, Canada. The study was supported in part by a discovery grant from the National Psoriasis Foundation and an operating grant from the Arthritis Society (YIO-16-394). The Psoriatic Disease Programme has been supported by a grant from the Krembil Foundation.

Competing interests KC reports grants from Arthritis Society, grants from National Psoriasis Foundation, during the conduct of the study. NS reports personal fees from Amgen, personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, personal fees from Eli Lilly, personal fees from Merck Sharpe & Dohme, personal fees from Novartis, personal fees from Novo Nordisk, personal fees from Pfizer, personal fees from Sanofi, outside the submitted work. IBM reports grants and personal fees from Abbvie, grants and personal fees from BMS, grants and personal fees from Janssen, grants and personal fees from Pfizer, grants and personal fees from Novartis, grants and personal fees from UCB, grants and personal fees from Eli Lilly, outside the submitted work. VC reports grants and personal fees from Amgen, grants and personal fees from Abbvie, grants, personal fees and other from Eli Lilly, personal fees from Janssen, personal fees from Novartis, personal fees from Pfizer, personal fees from UCB, personal fees from BMS, outside the submitted work. PH reports grants from Arthritis Society, during the conduct of the study. DDG reports grants and personal fees from Abbvie, grants and personal fees from Amgen, personal fees from BMS, grants and personal fees from Celgene, grants and personal fees from Eli Lilly, personal fees from Galapagos, personal fees from Gilead, grants and personal fees from Novartis, grants and personal fees from Pfizer, grants and personal fees from UCB, outside the submitted work. VP reports advisory work for Pfizer, AbbVie, Janssen, UCB, Novartis, Almirall and Celgene. VP has received honoraria from Kyowa Kirin Co. In his role as Department Division Director of Dermatology at the University of Toronto, VP has received departmental support from AbbVie, Bausch Health (formerly Valeant), Celgene, Janssen, LEO Pharma, Lilly, NAOS, Novartis, Pfizer, Pierre-Fabre and Sanofi in the past 3 years. LE reports grants from Arthritis Society, grants from National Psoriasis Foundation, grants from Ontario Ministry of Research Innovation and Science, during the conduct of the study. K-AL, SA, RW, RJC have no competing interests to declare.

Patient consent for publication Not required.

Ethics approval The study was approved by the University Health Network Ethics Board (08-0630) and all patients gave their informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information. Not applicable.

terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs
Dafna D Gladman http://orcid.org/0000-0002-9074-0592
Lihi Eder http://orcid.org/0000-0002-1473-1715

REFERENCES

1 Eder L, Wu Y, Chandran V, *et al*. Incidence and predictors for cardiovascular events in patients with psoriatic arthritis. *Ann Rheum Dis* 2016;75:1680–6.
2 Miller IM, Ellervik C, Yazdanyar S, *et al*. Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. *J Am Acad Dermatol* 2013;69:1014–24.
3 Gisterå A, Hansson GK. The immunology of atherosclerosis. *Nat Rev Nephrol* 2017;13:368–80.
4 Tam L-S, Kitas GD, González-Gay MA. Can suppression of inflammation by anti-TNF prevent progression of subclinical atherosclerosis in inflammatory arthritis? *Rheumatology* 2014;53:1108–19.
5 Siegel D, Devaraj S, Mitra A, *et al*. Inflammation, atherosclerosis, and psoriasis. *Clin Rev Allergy Immunol* 2013;44:194–204.
6 Szentpetery A, Haroon M, FitzGerald O. Cardiovascular comorbidities in psoriatic disease. *Rheumatol Ther* 2020;7:5–17.
7 Wilson PW, D'Agostino RB, Levy D, *et al*. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837–47.
8 Colaco K, Ocampo V, Ayala AP, *et al*. Predictive utility of cardiovascular risk prediction algorithms in inflammatory rheumatic diseases: a systematic review. *J Rheumatol* 2020;47:928–38.
9 Eder L, Chandran V, Gladman DD. The Framingham risk score underestimates the extent of subclinical atherosclerosis in patients with psoriatic disease. *Ann Rheum Dis* 2014;73:1990–6.
10 Eder L, Harvey P, Chandran V, *et al*. Gaps in diagnosis and treatment of cardiovascular risk factors in patients with psoriatic disease: an international multicenter study. *J Rheumatol* 2018;45:378–84.
11 Würtz P, Havulinna AS, Soininen P, *et al*. Metabolite profiling and cardiovascular event risk: a prospective study of 3 population-based cohorts. *Circulation* 2015;131:774–85.
12 Mora S, Glynn RJ, Ridker PM. High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. *Circulation* 2013;128:1189–97.
13 Welsh P, Rankin N, Li Q, *et al*. Circulating amino acids and the risk of macrovascular, microvascular and mortality outcomes in individuals with type 2 diabetes: results from the advance trial. *Diabetologia* 2018;61:1581–91.
14 Fischer K, Kettunen J, Würtz P, *et al*. Biomarker profiling by nuclear magnetic resonance spectroscopy for the prediction of all-cause mortality: an observational study of 17,345 persons. *PLoS Med* 2014;11:e1001606.
15 Ritchie SC, Würtz P, Nath AP, *et al*. The biomarker GlycA is associated with chronic inflammation and predicts long-term risk of severe infection. *Cell Syst* 2015;1:293–301.
16 Wang TJ, Larson MG, Vasan RS, *et al*. Metabolite profiles and the risk of developing diabetes. *Nat Med* 2011;17:448–53.
17 Wang J, Stančáková A, Soininen P, *et al*. Lipoprotein subclass profiles in individuals with varying degrees of glucose tolerance: a population-based study of 9399 Finnish men. *J Intern Med* 2012;272:562–72.
18 Stancáková A, Civelek M, Saleem NK, *et al*. Hyperglycemia and a common variant of GCKR are associated with the levels of eight amino acids in 9,369 Finnish men. *Diabetes* 2012;61:1895–902.
19 Yan D, Afifi L, Jeon C, *et al*. The metabolomics of psoriatic disease. *Psoriasis* 2017;7:1–15.
20 Kamleh MA, Snowden SG, Grapov D, *et al*. LC-MS metabolomics of psoriasis patients reveals disease severity-dependent increases in circulating amino acids that are ameliorated by anti-TNFα treatment. *J Proteome Res* 2015;14:557–66.
21 Kang H, Li X, Zhou Q, *et al*. Exploration of candidate biomarkers for human psoriasis based on gas chromatography-mass spectrometry serum metabolomics. *Br J Dermatol* 2017;176:713–22.
22 D'Agostino RB, Vasan RS, Pencina MJ, *et al*. General cardiovascular risk profile for use in primary care: the Framingham heart study. *Circulation* 2008;117:743–53.
23 Soininen P, Kangas AJ, Würtz P, *et al*. Quantitative serum nuclear magnetic resonance metabolomics in cardiovascular epidemiology and genetics. *Circ Cardiovasc Genet* 2015;8:192–206.
24 Soininen P, Kangas AJ, Würtz P, *et al*. High-throughput serum NMR metabonomics for cost-effective holistic studies on systemic metabolism. *Analyst* 2009;134:1781–5.
25 Würtz P, Kangas AJ, Soininen P, *et al*. Quantitative serum nuclear magnetic resonance metabolomics in large-scale epidemiology: a primer on -Omic technologies. *Am J Epidemiol* 2017;186:1084–96.
26 Binder H, Allignol A, Schumacher M, *et al*. Boosting for high-dimensional time-to-event data with competing risks. *Bioinformatics* 2009;25:890–6.
27 Binder H. CoxBoost: COX models by likelihood based boosting for a single survival endpoint or competing risks. R package version 1.4, 2013. Available: https://CRAN.R-project.org/package=CoxBoost
28 Blanche P, Dartigues J-F, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. *Stat Med* 2013;32:5381–97.
29 Blanche P, Proust-Lima C, Loubère L, *et al*. Quantifying and comparing dynamic predictive accuracy of joint models for longitudinal marker and time-to-event in presence of censoring and competing risks. *Biometrics* 2015;71:102–13.
30 Fine JP, Gray RJ. A proportional hazards model for the Subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
31 Gerds T, Ozenne B. riskRegression: risk regression models and prediction scores for survival analysis with competing risks. R package version 2019.11.03, 2019. Available: https://CRAN.R-project.org/package=riskRegression
32 Tukiainen T, Kettunen J, Kangas AJ, *et al*. Detailed metabolic and genetic characterization reveals new associations for 30 known lipid loci. *Hum Mol Genet* 2012;21:1444–55.
33 Würtz P, Raiko JR, Magnussen CG, *et al*. High-throughput quantification of circulating metabolites improves prediction of subclinical atherosclerosis. *Eur Heart J* 2012;33:2307–16.
34 Do R, Willer CJ, Schmidt EM, *et al*. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet* 2013;45:1345–52.
35 Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet* 2014;384:626–35.
36 Ip S, Lichtenstein AH, Chung M, *et al*. Systematic review: association of low-density lipoprotein subfractions with cardiovascular outcomes. *Ann Intern Med* 2009;150:474–84.
37 Benn M, levels AB. Apolipoprotein B levels, ApoB alleles, and risk of ischemic cardiovascular disease in the general population, a review. *Atherosclerosis* 2009;206:17–30.
38 Welsh C, Celis-Morales CA, Brown R, *et al*. Comparison of conventional lipoprotein tests and apolipoproteins in the prediction of cardiovascular disease. *Circulation* 2019;140:542–52.
39 Ference BA, Kastelein JJP, Ray KK, *et al*. Association of Triglyceride-Lowering LPL variants and LDL-C-Lowering LDLR variants with risk of coronary heart disease. *JAMA* 2019;321:364–73.
40 Ma C, Harskamp CT, Armstrong EJ, *et al*. The association between psoriasis and dyslipidaemia: a systematic review. *Br J Dermatol* 2013;168:486–95.
41 Ramezani M, Zavattaro E, Sadeghi M. Evaluation of serum lipid, lipoprotein, and apolipoprotein levels in psoriatic patients: a systematic review and meta-analysis of case-control studies. *Postepy Dermatol Alergol* 2019;36:692–702.
42 Connelly MA, Otvos JD, Shalaurova I, *et al*. GlycA, a novel biomarker of systemic inflammation and cardiovascular disease risk. *J Transl Med* 2017;15:219.
43 Akinkuolie AO, Buring JE, Ridker PM, *et al*. A novel protein glycan biomarker and future cardiovascular disease events. *J Am Heart Assoc* 2014;3:e001221.
44 Joshi AA, Lerman JB, Aberra TM, *et al*. GlycA is a novel biomarker of inflammation and subclinical cardiovascular disease in psoriasis. *Circ Res* 2016;119:1242–53.
45 Felig P, Marliss E, Cahill GF. Plasma amino acid levels and insulin secretion in obesity. *N Engl J Med Overseas Ed* 1969;281:811–6.
46 Chen S, Akter S, Kuwahara K, *et al*. Serum amino acid profiles and risk of type 2 diabetes among Japanese adults in the Hitachi health study. *Sci Rep* 2019;9:7010.
47 JE H, Larson MG, Ghorbani A. Metabolomic profiles of body mass index in the Framingham heart study reveal distinct cardiometabolic phenotypes. *PLoS One* 2016;11:e0148361.
48 Kopple JD. Phenylalanine and tyrosine metabolism in chronic kidney failure. *J Nutr* 2007;137:1586S–90. discussion 97S-98S6.
49 Druml W, Roth E, Lenz K, *et al*. Phenylalanine and tyrosine metabolism in renal failure: dipeptides as tyrosine source. *Kidney Int Suppl* 1989;27:S282–6.
50 Wan J, Wang S, Haynes K, *et al*. Risk of moderate to advanced kidney disease in patients with psoriasis: population based cohort study. *BMJ* 2013;347:f5961.
51 Solomon DH, Love TJ, Canning C, *et al*. Risk of diabetes among patients with rheumatoid arthritis, psoriatic arthritis and psoriasis. *Ann Rheum Dis* 2010;69:2114–7.
52 Wang TJ. Assessing the role of circulating, genetic, and imaging biomarkers in cardiovascular risk prediction. *Circulation* 2011;123:551–65.
53 Saravanan P, Davidson NC, Schmidt EB, *et al*. Cardiovascular effects of marine omega-3 fatty acids. *The Lancet* 2010;376:540–50.

CLINICAL SCIENCE

Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial

Anna Molto ,[1,2] Clementina López-Medina ,[2,3] Filip E Van den Bosch ,[4] Annelies Boonen ,[5,6] Casper Webers,[5,6] Emanuelle Dernis,[7] Floris A van Gaalen,[8] Martin Soubrier,[9] Pascal Claudepierre,[10,11] Athan Baillet ,[12,13] Mirian Starmans-Kool,[14] Anneke Spoorenberg,[15] Peggy Jacques ,[4,16] Philippe Carron ,[16,17] Rik Joos,[18] Jan Lenaerts,[19] Laure Gossec ,[20,21] Sophie Pouplin,[22] Adeline Ruyssen-Witrand,[23,24] Laetitia Sparsa,[25] Astrid van Tubergen ,[26] Désirée van der Heijde ,[27] Maxime Dougados[1,2]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2020-219585).

For numbered affiliations see end of article.

Correspondence to
Dr Anna Molto, Rheumatology, Hospital Cochin, Paris 75014, France; anna.molto@aphp.fr

Received 24 November 2020
Revised 16 April 2021
Accepted 18 April 2021
Published Online First 6 May 2021

► http://dx.doi.org/10.1136/annrheumdis-2021-220603

To cite: Molto A, López-Medina C, Van den Bosch FE, *et al*. *Ann Rheum Dis* 2021;**80**:1436–1444.

ABSTRACT

Objectives To compare the benefits of a tight-control/treat-to-target strategy (TC/T2T) in axial spondyloarthritis (axSpA) with those of usual care (UC).

Methods Pragmatic, prospective, cluster-randomised, controlled, open, 1-year trial (NCT03043846). 18 centres were randomised (1:1). Patients met Axial Spondylo Arthritis International Society (ASAS) criteria for axSpA, had an Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥2.1, received non-optimal treatment by non-steroidal anti-inflammatory drugs and were biologic-naive.

Interventions (1) *TC/T2T*: visits every 4 weeks and prespecified strategy based on treatment intensification until achieving target (ie, ASDAS <2.1); (2) *UC:* visits every 12 weeks and treatment at the rheumatologist's discretion.

Main outcome Percentage of patients with a ≥30% improvement on the ASAS-Health Index (ASAS-HI). Other efficacy outcomes and adverse events were recorded. A health economic evaluation was performed.

Statistical analysis Two-level mixed models were used to estimate efficacy outcomes. Cost-effectiveness was assessed by the incremental cost per quality-adjusted life-year (QALY) gained for TC/T2T versus UC.

Results 160 patients were included (80/group). Mean (SD) age was 37.9 (11.0) years and disease duration was 3.7 (6.2) years; 51.2% were men. ASDAS at inclusion was 3.0 (0.7), and ASAS-HI was 8.6 (3.7). ASAS-HI improved by ≥30% in 47.3% of the TC/T2T arm and in 36.1% of those receiving UC (non-significant). All secondary efficacy outcomes were more frequent in the TC/T2T arm, although not all statistically significant. Safety was similar in both arms. From a societal perspective, TC/T2T resulted in an additional 0.04 QALY, and saved €472 compared with UC.

Conclusion TC/T2T was not significantly superior to UC for the primary outcome, while many secondary efficacy outcomes favoured it, had a similar safety profile and was favourable from a societal health economic perspective.

Trial registration number NCT03043846.

Key messages

What is already known about this subject?

- Treat-to-target (T2T) has demonstrated to be an efficacious approach in rheumatic inflammatory diseases such as rheumatoid arthritis and psoriatic arthritis.
- Recommendations for the management of axial spondyloarthritis (axSpA) have been published, including the recommendation to apply a T2T approach in this disease, despite the lack of evidence of the utility of such approach in this disease, compared with usual care (UC).

What does this study add?

- This is the first study evaluating the efficacy of a treat-to-target and tight control (TC) approach in axSpA compared with UC.
- Overall, in this setting of expert centres in spondyloarthritis, UC resulted in very good outcomes for a substantial number of patients.
- Although the primary outcome measure was not achieved, response rates between the two treatment groups differed by 11% in favour of TC/T2T.
- Despite the higher prescription rate of biologics in the TC/T2T arm, safety profiles were similar across arms, and the TC/T2T arm had a favourable outcome from a societal health economic perspective.

How might this impact on clinical practice?

- This trial did not prove that a TC/T2T approach is significantly better than UC for the primary outcome, while many secondary efficacy outcomes favoured it, had a similar safety profile and was favourable from a societal health economic perspective at 1 year.
- This suggests that a TC/T2T approach might be beneficial in axSpA, but other strategy trials for this disease aiming to evaluate the efficacy of TC/T2Tin this setting are needed to build on our findings.

INTRODUCTION

Disease activity in axial spondyloarthritis (axSpA) is assessed by measuring inflammation, with composite indices such as the completely patient-reported Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[1] or the Ankylosing Spondylitis Disease Activity Score (ASDAS).[2] The ASDAS includes both patient-reported outcomes (PRO) and C-reactive protein (CRP), and is the preferred outcome for axSpA.[3] Moreover, several ASDAS thresholds categorising disease activity have been proposed and validated: a score <2.1 means low disease activity and ≥2.1 means active disease.[4 5]

The ASAS and European League Against Rheumatism (EULAR) societies have issued recommendations for the management of axSpA[6] and indications for the pharmacological interventions depend on disease activity. The two major categories of pharmacological treatments are non-steroidal anti-inflammatory drugs (NSAIDs) and biologic disease-modifying antirheumatic drugs (bDMARDs), such as tumour necrosis factor inhibitors (TNFi) and IL-17 inhibitors (IL-17i). According to these latest recommendations,[6] TNFi can be prescribed to patients with active disease (evaluated by ASDAS or BASDAI) despite previous exposure to at least two NSAIDs for at least 4 weeks in total (unless these drugs are contraindicated or cause side effects). Moreover, the presence of either objective signs of structural damage on pelvic radiography or inflammation (ie, elevated CRP or abnormal MRI showing subchondral bone oedema at the sacroiliac joint) is required. Finally, the rheumatologist should be convinced that in a particular patient there is a favourable benefit/risk profile. If the first TNFi fails, a switch to another TNFi or IL-17i should be considered.

According to the treat-to-target (T2T) concept, a precise and predefined determination about the target to be reached is defined before treatment starts; more importantly, the patient and treating physician decide in advance to intensify the treatment until the target is reached, unless contraindicated. The concept of tight control (TC) calls for rapid assessment of both efficacy and safety of a new treatment in a patient. For safety, the time frame can be very short, should an adverse event (AE) occur. As part of the TC, the efficacy of NSAIDs for axSpA should be evaluated after 4 weeks of treatment and of TNFi and IL-17i after 12–16 weeks.

In medicine, the combination of TC and T2T (a TC/T2T strategy) has demonstrated benefits in some areas, in particular for hypertension[7] and diabetes.[8] In rheumatology, this strategy has proven to be effective in rheumatoid arthritis[9] and psoriatic arthritis,[10] although these trials defined both the target and the outcome according to disease activity. In contrast with the previous TC/T2T trials in rheumatology, and more in line with what has been published in other disciplines, we decided to differentiate the target (ie, disease activity) and the outcome by choosing as the primary outcome the consequence of disease activity (ie, impact on functioning and health).

Conducting trials in which the new treatment algorithm is actually a complex strategy can be very challenging, as it may be difficult for the staff involved in the study not to apply their recently acquired experience with the new treatment algorithm into their usual standard of care. One approach to overcome this issue is to conduct a cluster-randomised trial. In these studies, not patients but centres/investigators are randomised; therefore, all individuals belonging to a certain centre are assigned to either the new treatment or the usual care (UC). This reduces the likelihood of 'contamination' of the UC treatment, since no centre provides both TC/T2T and UC.[11]

No trial has yet evaluated the potential benefits of a TC/T2T strategy for patients with axSpA,[12] although experts have already recommended using this strategy in daily practice.[13] The objective of this trial was thus to compare its potential benefits with UC in patients with axSpA.

METHODS

Study design

This was a pragmatic, prospective, parallel, cluster-randomised (with the centre as the cluster), open, controlled (two arms) trial (TICOSPA—NCT03043846). This study was not considered interventional, as the treatment was either a standard of care approach according to the treating rheumatologist (UC arm) or a TC/T2T algorithm strictly following the current international scientific recommendations for axSpA management. The study duration of 1 year was considered sufficient to demonstrate the benefits of a particular strategy on symptoms. The study was conducted in agreement with local good clinical practice (GCP) and the Declaration of Helsinki.

Participants

Centres/Clusters

The first step was to screen for centres in three European countries (France, the Netherlands and Belgium). Each centre had to be willing to apply the treatment to which they would be allocated and thus willing to follow the predefined treatment strategy if allocated to the TC/T2T arm. Thus, in order to minimise the chances of protocol violations in the TC/T2T arm, we selected centres with a particular interest in spondyloarthritis and that were interested in the potential efficacy of T2T and would be willing to follow the TC/T2T algorithm if randomised to this arm. Before randomisation, all selected centres signed a written agreement to adhere to their allocated strategy.

Patients

Patients had to be adults younger than 65 years, with a diagnosis of axSpA according to their rheumatologist and fulfilling the ASAS classification criteria for axSpA.[14] At inclusion, disease had to be active (ie, ASDAS ≥2.1). In addition, patients should not have been optimally treated with NSAIDs (ie, they could not have received two full courses of NSAIDs at a daily full dose for at least 2 weeks each) and should not have contraindications to NSAIDs, be biologic-naive and not have received apremilast in the past 3 months. They also had to have a pelvic radiography and MRI of the sacroiliac joints available, as well as their HLAB27 status. All patients needed to understand the study objectives and to complete questionnaires. They also had to provide written consent.

Treatments

TC/T2T arm

Visits were scheduled every 4 weeks, and the strategy was prespecified, based on the current recommendations for axSpA management,[6] compiled in an electronic algorithm that guided treatment decisions at each visit, after collection and entry of the ASDAS in the electronic case report form (CRF). The target was an ASDAS <2.1 (ie, low disease activity[4]); although remission has been proposed as the preferred target in recommendations, low disease activity has been proposed as an alternative: an ASDAS <2.1 was selected by the steering committee as <1.3 was considered too stringent. If the target was not met, intensification of treatment was proposed to the investigator until the target was met. In all cases, but in particular with regard to bDMARD

prescriptions, the recommendation had to be consistent with the product labelling. If the recommendation was to initiate a TNFi, the investigator chose which TNFi to use, considering the country's reimbursement criteria. For the specific case of bDMARDs, safety was evaluated every 4 weeks, but, according to recommendations, efficacy (ie, whether ASDAS target was met) was evaluated at the visit occurring after at least 12 weeks after initiation. When the target was met, treatment continuation was recommended; if the patient was considered to have inactive disease (ie, ASDAS <1.3), acceptance of any recommendation to taper NSAIDs was based on a shared decision with the patient. The full algorithm providing the predetermined recommendations at each visit is available in online supplemental file 1 and also in the Protocol.

Usual care

Visits to assess study outcomes were scheduled every 12 weeks, and all treatment decisions, including frequency of follow-up, were left to the investigator's discretion.

Outcomes

All outcomes were assessed at the patient level.

Efficacy outcomes

Primary outcome: The validated ASAS-Health Index (ASAS-HI) is a 17-item questionnaire (range 0–17, with 17 representing the worst health) that represents the most important items of the ASAS Core Set of the International Classification of Functioning as well as five patient-reported outcome (PRO) items.[15] The primary outcome of the trial was the percentage of patients achieving an improvement of at least 30% in the ASAS-HI at the 1 year visit.

Secondary efficacy outcomes can be categorised in two groups: (1) Disease activity outcomes: ASDAS over time, ASDAS states (ie, low disease activity (LDA) and inactive disease (ID)) and changes (ie, major improvement (MI) and clinically important improvement (CII)),[4 5] ASAS responses (ASAS20, ASAS40),[16] ASAS partial remission, BASDAI, BASDAI 50,[17] Physician Global Assessment and CRP; (2) other PRO measures (Bath Ankylosing Score Global (BASG),[18] Patient' global assessment of disease activity, Visual Analogic Scale (VAS) of Fatigue), functioning and health (ASAS-HI as a continuous score, BASFI[19] and EQ-5D-5L[20]), work impairment (Work Productivity and Activity Impairment Questionnaire, WPAI),[21] and treatment (ASAS-NSAID score,[22] which aims to quantify the NSAID intake in a defined period of time, and bDMARD initiations).

Safety outcomes

All adverse events (AEs) that were cardiovascular, gastrointestinal or related to infections or allergies during patients' participation in the study were collected and recorded in the case report form, in accordance with EULAR recommendations.[23]

Resource utilisation and costs (cost–utility analysis)

At each visit, cost questionnaires were added, assessing healthcare resource utilisation (rheumatologist and other specialist visits, nurse, physiotherapist, and emergency department visits, and days in rehabilitation centres and hospitals) and work days (of paid work) missed in the past 12 weeks. Costs per healthcare resource category over the 48-week follow-up were calculated by multiplying the resource used by the Dutch unit costs, taken from the Dutch guideline for economic evaluations, and expressed in 2019 Euros[24] (online supplemental file 4). Productivity losses were valued by using the human capital method in the base-case analysis.

No structural-progression outcomes were evaluated in this study, as the 1-year period was deemed too short to observe any effect.

Sample size estimation

Sample size was calculated in two consecutive steps.

First step: The cluster design was not considered (ie, this calculation used a conventional approach, considering that randomisation would occur at the patient level). It was anticipated that in the UC arm, 25% of the patients would meet the definition of response (≥30% improvement in the ASAS-HI score after 1 year of follow-up). For an α risk of 5% and a β risk of 80%, with a bilateral test, 77 patients per arm were needed to demonstrate a 20-percentage-point difference among responders, that is, at least a 45% responder rate in the TC/T2T arm if the UC responder rate was 25%. For a uniform number of patients per centre, we aimed for a total sample of 160 patients (80 per arm).

Second step: The cluster-randomised design was considered by multiplying the estimated sample needed (ie, 160 patients) by an 'inflation factor' defined as $1+(m-1)*\rho$, where m is equal to the size of the cluster (in our study, the number of patients per centre=10) and ρ is the intracluster correlation, usually set at 0.05.[25] The inflation factor for our study was 1.45, and thus the sample needed to take the cluster-randomised design into account was 232 patients (116 patients per arm).

Randomisation and blinding

The 1:1 randomisation was cluster-based: a random number table was used to randomise centres instead of individuals. Centres allocated to the UC arm were blinded for the specific TC/T2T strategy (including treatment and frequency of assessments) in this trial until the end of the study. Separate investigator meetings on different days were organised for each arm.

This was an open study in the sense that centres were not blinded to the study arm to which they were allocated. Within each centre, consecutive patients meeting the inclusion criteria were screened and invited to participate: patients were not blinded but received different information letters, depending on the allocation of the centre in which they were included (one explaining the TC/T2T strategy and visit schedules, and the other the UC visit schedule).

Statistical methods

All statistical analyses were performed with the open-source software R, V.3.5.2,[26] and Stata SE release V.14.0.

The analysis population was the intention-to-treat population.

Efficacy analysis

A cluster-randomisation design must consider two main limitations. The first is that observations of groups of individuals from the same cluster have a lower variance. To take this into account, all the efficacy analyses first used a two-level mixed model with two random effects to estimate the percentage of responders or the change in outcome over the follow-up (ie, a cluster-adjusted model). The second limitation is that in this type of trial, randomisation occurs at the cluster level, while outcomes are assessed at the individual (patient) level. Therefore, to compensate for the potential imbalance of some covariates across treatment groups, we identified those that were not balanced and included them as adjustment factors in a second model otherwise identical to the first (ie, cluster and imbalance-adjusted model, presented

in detail in online supplemental file 3). The use of mixed-effects models enabled us to deal with the missing data by using maximum likelihood.[27]

Safety analysis

The number and types of AEs were described both globally and by study arm, as recommended by EULAR[28] for cardiovascular, infection-related and gastrointestinal events, as well as allergy (skin reactions and anaphylaxis).

Cost–utility analysis

A health economic evaluation from the perspectives of healthcare and of society (including also costs related to sick leave) was performed. In the base case, cumulative costs and time-averaged health utilities were calculated for each patient after multiple imputation of missing cost categories and EuroQol 5 domains and 5 levels (EQ-5D). Next, the incremental costs (iCosts) and effects (quality-adjusted life-years, iQALY) were used to calculate the incremental cost per QALY gained (incremental cost–utility ratio or ICUR; ICUR=iCosts/iQALY) and incremental net monetary benefit (iNMB; iNMB=iQALY*[willingness-to-pay threshold]–iCosts). To account for baseline differences in costs and QALYs between the study arms, these incremental costs and QALYs were baseline-adjusted by using seemingly unrelated regressions (SUREG). With SUREG, costs and effects can be modelled jointly within the same model, thereby taking their (expected) correlation into account.[29 30] For this analysis, SUREG was used with a robust variance estimator to reflect the clustering of the data. Finally, the conventional non-parametric bootstrapping method was considered inappropriate for estimating the CIs of the ICUR and cost-effectiveness acceptability curves, because it ignores the clustering of patients inherent to a cluster-randomised clinical trails (RCT). Instead, two-stage bootstrapping, which resamples clusters (first stage) *and* individuals (second stage), was performed.[31 32] As the cluster sizes were not balanced, a modified version[33] that allows for this imbalance was used to resample the current study population 5000 times. In addition to the base-case analysis, several sensitivity analyses were conducted. These assessed the impact of reducing bDMARD costs, a different valuation method for productivity losses (the friction cost approach, which considered only productivity losses during the 13-week friction period), the inclusion of costs of presenteeism (at-work productivity loss) and utility based on ASAS-HI (instead of EQ-5D).[34] For all analyses, both the societal perspective (including all costs) and the healthcare perspective (including only healthcare costs and excluding productivity losses) are presented. The willingness-to-pay threshold used to interpret the ICUR and to calculate the iNMB was set at €20 000/QALY, based on the level of health reported by the subjects in the current study and recommended Dutch thresholds.[35]

RESULTS

Participant flow

Eighteen centres (4 in Belgium, 10 in France and 4 in the Netherlands), all of them rheumatology departments with an expertise in SpA, were invited and agreed to participate. All centres signed an agreement to follow the treatment to which they were allocated. After randomisation, nine centres were allocated to the TC/T2T arm and nine to the UC arm.

During the recruitment period (from February 2017 to June 2019; dataset locked on August 2019), centres from the TC/T2T arm screened and included 80 patients, while centres from the UC arm screened 83 patients and included 80. The analysis population comprised 160 patients. After 1 year, one centre (UC arm) had not included any patient. At the patient level, in the TC/T2T arm, seven patients were lost to follow-up and one refused to continue the study; in the UC arm, three patients were lost to follow-up, four refused to continue and one was excluded because of a non-spondyloarthritis diagnosis during follow-up. In total, 144 patients (72 per arm) completed the last visit (figure 1 presents the study flow diagram, and online supplemental file 2 presents the flow diagram of the study at the cluster level).

Baseline data

The patients' mean age (SD) was 37.9 (11.0) years with a mean disease duration of 3.7 (6.2) years; 51.2% were men. Radiographic damage of the sacroiliac joints was found in 46.9% of patients, 81.9% had had MRI-positive sacroiliitis at least once, and 75.0% were HLA-B27+. Mean ASDAS at inclusion was 3.0 (0.7) and mean ASAS-HI was 8.6 (3.7). The study design resulted in a significant baseline imbalance of some variables at the patient level: patients from the TC/T2T arm had a university education, a history of anterior uveitis and a higher Physician Global Assessment significantly more often; they had a history of gastrointestinal events related to NSAID intake less often and fewer mean days in rehabilitation facilities in the 3 months before the study (see online supplemental file 3). These variables were therefore included as adjustment variables in the 'cluster and imbalance-adjusted model'. Baseline characteristics are presented in table 1.

Efficacy outcomes

The estimated percentages of patients achieving an improvement ≥30% on the ASAS-HI at the 1 year visit with the 'cluster and imbalance-adjusted model' was 47.3% in the TC/T2T arm and 36.1% in the UC arm. The estimated difference (11.2%, 95% CI 8.5% to 13.9%) was not statistically significant in either model (p=0.094 and p=0.079 for the 'cluster-adjusted' and 'cluster and imbalance-adjusted' models, respectively). Some estimated efficacy outcomes were significantly favouring the TC/T2T arm, for example, 76.5% vs 59.5% (p<0.05 with both models) for ASDAS low disease activity and 52.3% vs 34.7% (p<0.05 with both models) for the ASAS40 at 1 year (figure 2), but the majority did not reach a statistical significance (table 2). The ASAS-NSAID score was not significantly different between treatment arms. The prescription rate for biologics was initially lower in the TC/T2T arm, but was quickly (ie, within 30 days) significantly higher among these patients (56.2% vs 27.2%, p<0.01; online supplemental file 5).

Safety

Overall, 55 AEs were reported, 33 in the TC/T2T and 22 in the UC arm. The TC/T2T arm had more allergies (8 vs 1) mainly because of local skin reactions at the injection site. Both groups had a similar number of infections (15 vs 16 in the TC/T2T and UC arms, respectively), with 2 of them severe, both in the UC arm. Table 3 summarises all the AEs.

Cost–utility analysis

During this 48-week follow-up, there were more visits to rheumatologists and more days of bDMARDs used, but fewer visits to physical therapy, fewer days of rehabilitation care and especially fewer days of sick leave in the TC/T2T arm (online supplemental file 4).

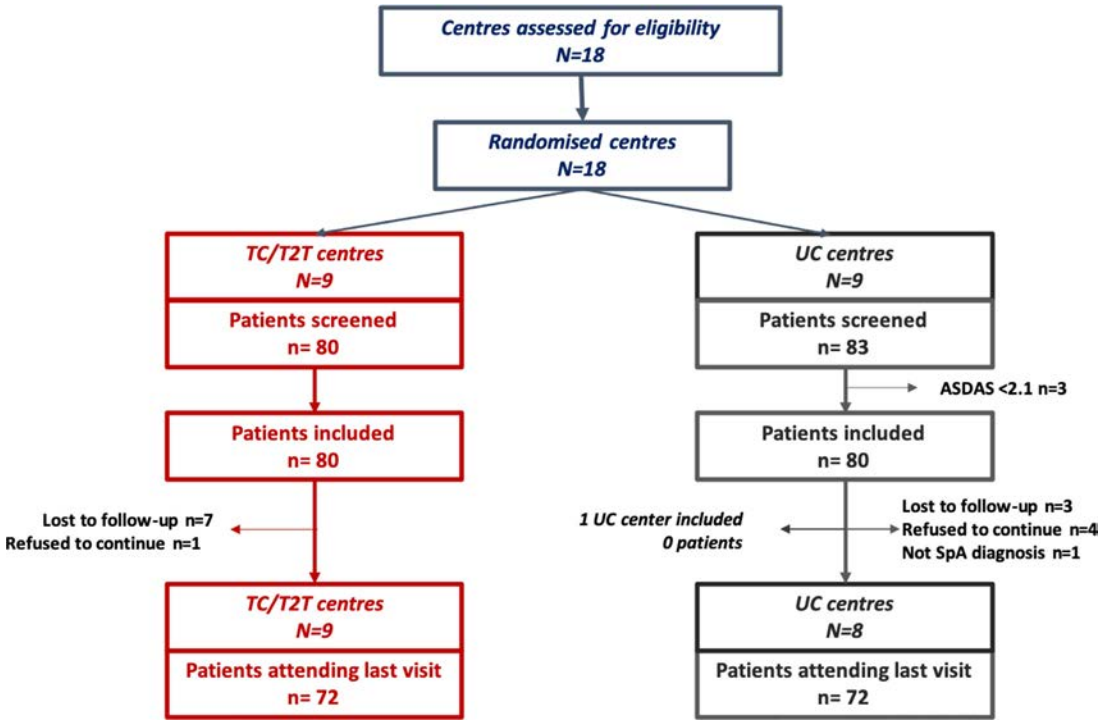


Figure 1 Flow chart of the study. ASDAS, Ankylosing Spondylitis Disease Activity Score; SpA, spondyloarthritis; TC/T2T, tight control and treat-to-target; UC, usual care.

In the unadjusted base-case analysis, TC/T2T dominated UC (iQALY 0.07; iCosts −€1472) from a societal perspective and was cost-effective with an ICUR of €11 538 (iQALY 0.07; iCosts €801) from a healthcare perspective. The baseline-adjusted and cluster-adjusted base-case analysis produced similar results, with TC/T2T dominating UC and being cost-effective with an ICUR of €19 430 from the societal and healthcare perspective, respectively. In bootstrapped adjusted analyses, the probability that TC/T2T would be cost-effective compared with UC was 72% from the societal perspective and 52% from the healthcare perspective, given a threshold for willingness-to-pay of €20 000/QALY.

In the sensitivity analyses, lower bDMARD costs favoured TC/T2T even more strongly, as expected. The estimate of productivity costs based on the friction cost approach (ie, considering only the first 13 weeks of absence) still favoured TC/T2T, as did inclusion of the presenteeism costs (ie, productivity loss while at work), both somewhat less strongly than the base case. Finally, using disease-specific utilities based on the ASAS-HI instead of the EQ-5D to calculate QALYs resulted in less favourable results for TC/T2T due to the smaller gain in QALYs (0.015–0.018) for TC/T2T relative to UC (table 4 and online supplemental file 4).

Table 1 Baseline characteristics of patients included in the two treatment arms

	TC/T2T (n=80)	UC (n=80)	Total (n=160)
Age (years)*	37.6 (10.8)	38.1 (11.4)	37.9 (11.0)
Sex (Male)	45 (56.2%)	37 (46.2%)	82 (51.2%)
Smoking status (current)	29 (36.2%)	32 (40.0%)	61 (38.1%)
University studies †	57 (71.2%)	42 (52.2%)	99 (61.9%)
Disease duration (years)	4.2 (6.56)	3.3 (5.83)	3.7 (6.20)
Radiographic sacroiliitis	42 (52.5%)	33 (41.2%)	75 (46.9%)
MRI sacroiliitis	63 (78.8%)	68 (85.0%)	131 (81.9%)
HLA B27 positive	62 (77.5%)	58 (72.5%)	120 (75.0%)
History of anterior uveitis†	16 (20.0%)	6 (7.5%)	22 (13.8%)
Good NSAID response	63 (78.8%)	55 (68.8%)	118 (73.8%)
ASDAS	3.0 (0.7)	3.0 (0.6)	3.0 (0.7)
BASDAI (n=80/79)	5.2 (1.7)	5.2 (1.9)	5.2 (1.8)
CRP (mg/L)	9.2 (9.8)	7.4 (10.5)	8.3 (10.1)
ASAS-Health Index (0–17) (n=80/78)	8.2 (3.8)	9.0 (3.6)	8.6 (3.70)
NSAID score (last 3 months)	32.7 (35.4)	37.5 (36.6)	35.1 (36.0)

*Numerical variables are presented as means (SD) and categorical variables as n (percentage).
†Significantly imbalanced variables; other imbalanced variables at baseline were gastrointestinal events in relation to NSAIDs, Physician Global and Rehabilitation days (see online supplemental file 3).
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; NSAID, non-steroidal anti-inflammatory drugs.

DISCUSSION

This is the first strategy trial evaluating the potential benefits of a TC/T2T strategy in patients with axSpA. This was a negative trial, in which the main outcome did not reach a statistically significant difference in both groups. Safety was similar in both arms, even though biologics were prescribed significantly more often in the TC/T2T arm and produced more local injection site allergic reactions in this arm. The health economic analysis also favoured the TC/T2T arm from the societal perspective and (although with a lower level of certainty) from the healthcare perspective as well.

Nevertheless, in almost all of the estimated efficacy outcomes scores and responses were in favour of the TC/T2T, even if most did not reach a statistical significance. Therefore, it is important to analyse the reasons behind the lack of a statistically significant difference between the groups for the main outcome measure. While some would consider this a negative trial and would argue that no further efficacy endpoints should be interpreted, this approach has been considered by some as overly simplistic in

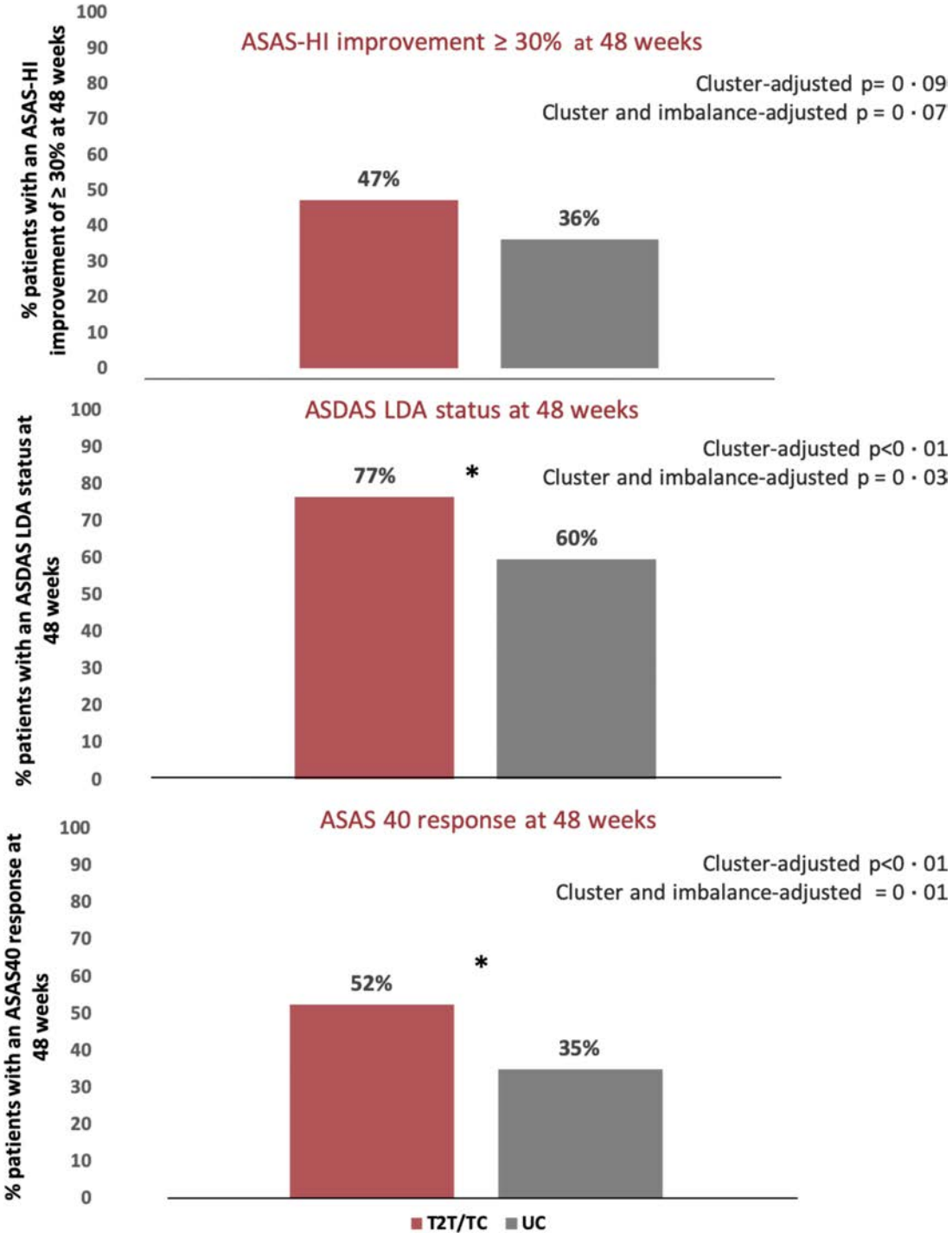


Figure 2 ASAS-HI improvement ≥30%, ASDAS LDA status and ASAS40 response estimated at 48 weeks. *Statistical significance. ASAS-HI, Axial Spondyloarthritis International Society-Health Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; LDA, low disease activity; T2T/TC, treat-to-target and tight control; UC, usual care.

the literature,[36] and in some cases, the presentation of all results is needed to guide appropriate clinical interpretation of the findings.

The first reason behind our not statistically significant results may be related to the choice of the outcome measure: in most strategy trials the target is usually defined by a relevant threshold in a factor that predisposes patients to that outcome, below which the risk of developing this outcome is abolished or significantly reduced. A good example of this can be found in a TC/T2T strategy in diabetes that aimed for a target of glycosylated haemoglobin below 7% and used a decreased rate of diabetic retinopathy as the primary objective.[11] Interestingly, in the two published T2T trials in rheumatology, the TICORA[9] and TICOPA[10] trials, both the outcome and the target were 'disease activity-related', that is, Disease Activity Score 28 (DAS28) and EULAR response in TICORA and minimal disease activity and American College of Rheumatology (ACR) 20 in TICOPA. To avoid the potential circularity, in TICOSPA the target was disease activity but the main outcome was a consequence of disease activity, that is, disease-specific functioning

Table 2 Estimated efficacy outcomes at the last study visit (week 48)

	Estimated outcomes at week 48			
	TC/T2T	UC	Cluster-adjusted model	Cluster and imbalance-adjusted model
ASAS-HI significant improvement	47.3%	36.1%	NS	NS
ASDAS LDA	76.5%	59.5%	<0.01	0.03
ASDAS ID	25.9%	18.7%	NS	NS
ASDAS CII	61.2%	46.0%	<0.01	0.02
ASDAS MI	16.5%	14.9%	NS	NS
ASAS40	52.3%	34.7%	<0.01	0.01
ASAS20	94.9%	85.9%	<0.01	0.03
BASDAI 50	79.0%	43.8%	0.01	0.03
Physician Global (0–10)	2.0 (0.2)	1.8 (0.2)	NS	NS
CRP (mg/L)	3.9 (1.4)	3.5 (1.5)	NS	NS
BASG (0–10)	2.6 (0.5)	3.4 (0.5)	NS	NS
BASFI (0–10)	1.7 (0.5)	2.4 (0.5)	NS	NS
EQ5D-5L	0.7 (0.1)	0.8 (0.1)	0.02	NS
ASAS-NSAID score	1.5 (2.2)	−4.9 (2.9)	NS	NS

ASAS-HI, ASAS-Health Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CII, clinically important improvement; EQ5D, EuroQol 5 domains and 5 levels; ID, inactive disease; LDA, low disease activity; MI, major improvement; NS, non-significant.

and health, measured by ASAS-HI. Furthermore, others may consider that our outcome was not ambitious enough and we should have aimed at reducing structural damage, like retinopathy for diabetes[8] or cardiovascular events (such as myocardial infarction or stroke) for hypertension.[7] However, keeping in mind the lower prevalence of axSpA (compared with diabetes and hypertension) and the slow progression rate in axSpA nowadays, it would have been very difficult to run such TC/T2T trial in axSpA.

Another reason behind this lack of statistically significant difference is the unexpected good results of the UC arm: in our initial hypothesis, we expected a 25% response in the UC group, while UC presented a 36% response rate. This can be explained by the open cluster-trial design, as only SpA expert centres, aware of the need for such a trial and of the TC/T2T recommendations could be selected to participate, and were thus probably applying recommendations in their 'usual care'. Also, we calculated the expected treatment effect as if the study was a trial against placebo (in which a 20% difference is usually used). Here, patients from the control group were not receiving a placebo. In the rheumatology literature, a 12% difference in response between two active-treatment groups has been set as the difference to be observed in non-inferiority head-to-head trials.[37–39]

Table 3 Adverse events observed during the trial

	Total (n=160)	T2T (n=80)	UC (n=80)
Total number of adverse events	55	33	22
Cardiovascular events	0	0	0
Allergies	9	8	1
Skin, local reaction	7	6	1
Anaphylactic reaction	2	2	0
Infection	31	15	16
Opportunistic infections	2	0	2
Viral	22	12	10
Severe infections	2	0	2
Gastrointestinal events	12	7	5

UC, usual care.

Alternatively, there is also the possibility that this trend observed across efficacy outcomes in favour of TC/T2T is not due to a true-positive effect but is either non-clinically relevant or only reflecting a higher placebo effect on the TC/T2T arm. Indeed, patients and centres were not blinded to the arm of treatment they were allocated to: patients from the TC/T2T arm received an information sheet in which it was stated that they would be receiving the 'state-of-art' of treatment, strictly following current recommendations; as all efficacy outcomes are patient-reported, it is also possible that the observed and estimated differences in favour of TC/T2T are only reflecting a placebo effect.

Nevertheless, in an era of cost-containment, the cost-utility analysis favoured the TC/T2T strategy, especially from the societal perspective. Results of the economic evaluation were different from those observed in the TICOPA[10] trial, where the active arm was significantly more expensive than the UC arm, despite iQALYs similar to those in TICOSPA. This might be explained by the partial offset in TICOSPA of the extra cost of bDMARDs and visits by the substantially lower costs due to reduced numbers of days of sick leave and of visits for physiotherapy and rehabilitation facilities. The costs per unit of the different health resources, such as visits to the rheumatologist, varied according to the study setting: the UK for TICOPA, compared with Dutch true costs, adjusted for purchasing power parities for Belgium and France, for TICOSPA. This might have driven differences between the studies and limited comparisons. Furthermore, with the arrival of biosimilars, the costs of bDMARDs decreased substantially compared with TICOPA. Moreover, patients from the UC arm used rehabilitation and physical therapy more often at baseline, and this trend continued during the study. Our cluster-randomisation design of the trial may explain this difference: different habits in different centres may have led to differences in costs.

Overall, in this setting of expert centres in SpA, UC resulted in very good outcomes for a substantial number of patients. Although the primary outcome measure was not achieved, with response rates between the two treatment groups differed by 11% in favour of TC/T2T. Despite the higher prescription rate of biologics in the TC/T2T arm, safety profiles were similar across arms, and the TC/T2T arm had a favourable outcome from a

Table 4 Cost–utility analyses

	Perspective	Adjustment	iCosts	iQALY	ICUR	iNMB*	p20†	p50†
Base-case analyses								
Unadjusted	Societal	None	−€1472	0.069	Dominates UC	€2860	0.85	0.92
Adjusted	Healthcare	None	€801	0.069	€11 538/QALY (NE)	€587	0.69	0.91
	Societal	Baseline costs/effects	−€472	0.041	Dominates UC	€1295	0.72	0.83
	Healthcare	Baseline costs/effects	€789	0.041	€19 430/QALY (NE)	€23	0.52	0.78
Sensitivity analyses								
bDMARD discount (25%)	Societal	Baseline costs/effects	−€856	0.041	Dominates UC	€1678	0.78	0.86
	Healthcare	Baseline costs/effects	€406	0.041	€9888/QALY (NE)	€415	0.68	0.86
bDMARD discount (50%)	Societal	Baseline costs/effects	−€1239	0.041	Dominates UC	€2060	0.82	0.88
	Healthcare	Baseline costs/effects	€23	0.042	€553/QALY (NE)	€809	0.86	0.91
ASAS-HI utility	Societal	Baseline costs/effects	−€466	0.018	Dominates UC	€817	0.64	0.67
	Healthcare	Baseline costs/effects	€793	0.015	€51 938/QALY (NE)	−€487	0.29	0.48
Friction cost approach‡	Societal	Baseline costs/effects	€183	0.042	€4400/QALY (NE)	€648	0.63	0.79
Costs of presenteeism included	Societal	Baseline costs/effects	−€876	0.040	Dominates UC	€1679	0.67	0.76

*For lambda (willingness-to-pay threshold)=€20 000/QALY.
†Probability that TC/T2T is cost-effective for willingness-to-pay thresholds (lambda) of €20 000/QALY or €50 000/QALY (p20 or p50, respectively).
‡For the friction cost approach, absenteeism (sick leave) that lasts longer than the friction period (13 weeks) is not included in the costs.
iCosts, incremental costs; iQALY, incremental QALY; NE, northeast (position of intervention in cost-effectiveness plane, comparator at centre [0,0].

societal health economic perspective. This suggests that a TC/T2T approach might be beneficial in axSpA, but other strategy trials for this disease aiming to evaluate the efficacy of TC/T2Tin this setting are needed to build on our findings.

Author affiliations
[1]Rheumatology Department, Hospital Cochin, Paris, France
[2]ECAMO team, INSERM U1153, Paris, France
[3]Rheumatology Department, Reina Sofia University Hospital, Cordoba, Andalucía, Spain
[4]Rheumatology Department, University Hospital Ghent, Gent, Oost-Vlaanderen, Belgium
[5]Department of Internal Medicine, Division of Rheumatology, Maastricht University, Maastricht, The Netherlands
[6]Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands
[7]Rheumatology Department, Le Mans Hospital, Le Mans, France
[8]Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[9]Rheumatology, CHU, Clermont-Ferrand, France
[10]Rheumatology, Henri Mondor Hospital Rheumatology Service, Creteil, France
[11]EpiDermE, Université Paris Est Créteil, Créteil, France
[12]Rheumatology, Hopital Sud, Echirolles, France
[13]GREPI EA7408, Universite Grenoble Alpes, Saint-Martin-d'Heres, France
[14]Rheumatology, Zuyderland Medical Centre Heerlen, Heerlen, The Netherlands
[15]Rheumatology & Clinical Immunology, University Medical Centre Groningen, Groningen, The Netherlands
[16]Rheumatology, VIB-UGent Center for Inflammation Research, Zwijnaarde, Belgium
[17]Rheumatology, University Hospital Ghent, Gent, Belgium
[18]Rheumatology, ZNA UKJA, Antwerpen, Belgium
[19]Rheumatology, Reumainstituut Hasselt, Hasselt, Belgium
[20]Rheumatology Department, University Hospital Pitié Salpêtrière, Paris, France
[21]Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France
[22]Rheumatology, Bois-Guillaume CHU, Rouen, France
[23]Rheumatology, University Hospital Centre Toulouse, Toulouse, France
[24]Paul Sabatier University, Toulouse, France
[25]Rheumatology department, Hospital Centre Mulhouse, Mulhouse, France
[26]Department of Medicine, Division of Rheumatology, Maastricht University Medical Center, Maastricht, The Netherlands
[27]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

Twitter Anna Molto @annamolto and Philippe Carron @PhilippeCarron

Acknowledgements The authors would like to thank PNSResearch for organising the logistics of implementing the study in the three countries.

Contributors All authors contributed to the manuscript as follows: AM, CL-M, MD, FEVdB, DvdH AB: conception, design and interpretation of data. AM, CL-M, CW: analysis of the data. AM drafted the manuscript. All authors critically reviewed the results and contributed to the interpretation of data. All authors read and approved the final manuscript, as well as the answer to the reviewers' comments.

Funding UCB provided an unrestricted grant for this study, but had no role in providing any drug, or in the study design, data collection, data analysis, data interpretation or writing of the report.

Competing interests Dr van Tubergen reports grants and personal fees from Novartis, grants from Pfizer, grants from UCB, grants from Biogen, grants from AbbVie, outside the submitted work. Dr van der Heijde reports personal fees from AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Cyxone, Daiichi, Eisai, Eli-Lilly, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, UCB Pharma, outside the submitted work; and Director of Imaging Rheumatology bv. Dr van Gaalen reports grants from Stichting vrienden van Sole Mio, grants from Stichting ASAS, grants and personal fees from Novartis, grants from UCB, personal fees from MSD, personal fees from AbbVie, personal fees from Bristol Myers Squibb, outside the submitted work. AB received a research grant to her department from AbbVie, consultation fees from Eli Lilly and Galapagos and a speakers fee from UCB, all paid to her department. Dr Van den Bosch reports personal fees from AbbVie, personal fees from Celgene, personal fees from Eli Lilly, personal fees from Galapagos, personal fees from Janssen, personal fees from Novartis, personal fees from Pfizer, personal fees from UCB, outside the submitted work. Dr Claudepierre reports personal fees from Roche Chugai, Novartis, Pfizer, MSD, grants from Roche Chugai, Novartis, Pfizer, UCB, MSD, AbbVie, Lilly, Celgene, Janssen, BMS, outside the submitted work. Dr Molto reports grants from UCB during the conduct of the study; personal fees from AbbVie, grants and personal fees from UCB, personal fees from BMS, grants and personal fees from Pfizer, grants and personal fees from MSD, personal fees from Novartis, personal fees from Gilead, personal fees from Lilly, outside the submitted work. Dr Gossec reports grants from Amgen, Lilly, Janssen, Pfizer, Sandoz, Sanofi, Galapagos, personal fees from AbbVie, Amgen, BMS, Biogen, Celgene, Gilead, Janssen, Lilly, Novartis, Pfizer, Samsung Bioepis, Sanofi-Aventis, UCB, outside the submitted work. Dr Dougados reports grants from UCB, during the conduct of the study; grants and personal fees from AbbVie, grants and personal fees from Pfizer, grants and personal fees from Lilly, grants and personal fees from Novartis, grants and personal fees from Roche, grants and personal fees from BMS, grants and personal fees from Merck, outside the submitted work. Dr Dernis, Dr Ruyssen-Witrand, Dr Lenaerts, Dr Lopez-Medina, Dr Sparsa, Dr Starmans-Kool, Dr C Webers, Dr Pouplin, Dr Soubrier and Dr Joos have nothing to declare.

Patient consent for publication Not required.

Ethics approval The study was approved by the ethics committee CPP Ile de France III (Réf. Am7156-1-S.C.3394). All patients gave their informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Anna Molto http://orcid.org/0000-0003-2246-1986
Clementina López-Medina http://orcid.org/0000-0002-2309-5837
Filip E Van den Bosch http://orcid.org/0000-0002-3561-5932
Annelies Boonen http://orcid.org/0000-0003-0682-9533
Athan Baillet http://orcid.org/0000-0001-6006-2519
Peggy Jacques http://orcid.org/0000-0001-9227-257X
Philippe Carron http://orcid.org/0000-0001-9254-6171
Laure Gossec http://orcid.org/0000-0002-4528-310X
Astrid van Tubergen http://orcid.org/0000-0001-8477-0683
Désirée van der Heijde http://orcid.org/0000-0002-5781-158X

REFERENCES

1 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.
2 Lukas C, Landewé R, Sieper J, *et al*. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009;68:18–24.
3 van der Heijde D, Braun J, Dougados M, *et al*. Sensitivity and discriminatory ability of the ankylosing spondylitis disease activity score in patients treated with etanercept or sulphasalazine in the ASCEND trial. *Rheumatology* 2012;51:1894–905.
4 Machado PM, Landewé R, Heijde Dvander, *et al*. Ankylosing spondylitis disease activity score (ASDAS): 2018 update of the nomenclature for disease activity states. *Ann Rheum Dis* 2018;77:1539–40.
5 Machado P, Landewé R, Lie E, *et al*. Ankylosing spondylitis disease activity score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis* 2011;70:47–53.
6 van der Heijde D, Ramiro S, Landewé R, *et al*. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017;76:978–91.
7 SPRINT Research Group, Wright JT, Williamson JD, *et al*. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373:2103–16.
8 ACCORD Study Group, ACCORD Eye Study Group, Chew EY, *et al*. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 2010;363:233–44.
9 Grigor C, Capell H, Stirling A, *et al*. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004;364:263–9.
10 Coates LC, Moverley AR, McParland L, *et al*. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet* 2015;386:2489–98.
11 Meurer WJ, Lewis RJ. Cluster randomized trials: evaluating treatments applied to groups. *JAMA* 2015;313:2068–9.
12 Schoels MM, Braun J, Dougados M, *et al*. Treating axial and peripheral spondyloarthritis, including psoriatic arthritis, to target: results of a systematic literature search to support an international treat-to-target recommendation in spondyloarthritis. *Ann Rheum Dis* 2014;73:238–42.
13 Smolen JS, Braun J, Dougados M, *et al*. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international Task force. *Ann Rheum Dis* 2014;73:6–16.
14 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.
15 Kiltz U, van der Heijde D, Boonen A, *et al*. Development of a health index in patients with ankylosing spondylitis (ASAS HI): final result of a global initiative based on the ICF guided by ASAS. *Ann Rheum Dis* 2015;74:830–5.
16 Brandt J, Listing J, Sieper J, *et al*. Development and preselection of criteria for short term improvement after anti-TNF alpha treatment in ankylosing spondylitis. *Ann Rheum Dis* 2004;63:1438–44.
17 Rudwaleit M, Listing J, Brandt J, *et al*. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. *Ann Rheum Dis* 2004;63:665–70.
18 Jones SD, Steiner A, Garrett SL, *et al*. The Bath ankylosing spondylitis patient global score (BAS-G). *Br J Rheumatol* 1996;35:66–71.
19 Calin A, Garrett S, Whitelock H, *et al*. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath ankylosing spondylitis functional index. *J Rheumatol* 1994;21:2281–5.
20 Tsang HHL, Cheung JPY, Wong CKH, *et al*. Psychometric validation of the EuroQoL 5-dimension (EQ-5D) questionnaire in patients with spondyloarthritis. *Arthritis Res Ther* 2019;21:41.
21 Reilly MC, Gooch KL, Wong RL, *et al*. Validity, reliability and responsiveness of the work productivity and activity impairment questionnaire in ankylosing spondylitis. *Rheumatology* 2010;49:812–9.
22 Dougados M, Simon P, Braun J, *et al*. ASAS recommendations for collecting, analysing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis. *Ann Rheum Dis* 2011;70:249–51.
23 Baillet A, Gossec L, Carmona L, *et al*. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. *Ann Rheum Dis* 2016;75:965–73.
24 National Health Care Institute. Ministerie van Volksgezondheid W en S. Guideline for economic evaluations in healthcare, 2016. Available: https://english.zorginstituutnederland.nl/publications/reports/2016/06/16/guideline-for-economic-evaluations-in-healthcare [Accessed 29 Jun 2020].
25 Hemming K, Girling AJ, Sitch AJ, *et al*. Sample size calculations for cluster randomised controlled trials with a fixed number of clusters. *BMC Med Res Methodol* 2011;11:102.
26 R: the R project for statistical computing. Available: https://www.r-project.org/ [Accessed 14 May 2020].
27 Allison PD. 312-2012: handling missing data by maximum likelihood 2012;21.
28 Baillet A, Gossec L, Carmona L, *et al*. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. *Ann Rheum Dis* 2016;75:965–73.
29 Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Econ* 2004;13:461–75.
30 Pearson. Greene, Econometric analysis. Available: https://www.pearson.com/us/higher-education/product/Greene-Econometric-Analysis-7th-Edition/9780131395381.html [Accessed 14 May 2020].
31 Davison AC, Hinkley DV. *Bootstrap methods and their application*. Cambridge Core, 1997.
32 Flynn TN, Peters TJ. Use of the bootstrap in analysing cost data from cluster randomised trials: some simulation results. *BMC Health Serv Res* 2004;4:33.
33 Gomes M, Ng ES-W, Grieve R, *et al*. Developing appropriate methods for cost-effectiveness analysis of cluster randomized trials. *Med Decis Making* 2012;32:350–61.
34 Essers I, Hiligsmann M, Kiltz U, *et al*. Development of one general and six country-specific algorithms to assess societal health utilities based on ASAS HI. *RMD Open* 2019;5:e000872.
35 Zorginstituut Nederland. Ministerie van Volksgezondheid W en S. Ziektelast in de praktijk - De theorie en praktijk van het berekenen van ziektelast bij pakketbeoordelingen, 2018. Available: https://www.zorginstituutnederland.nl/publicaties/rapport/2018/05/07/ziektelast-in-de-praktijk [Accessed 29 Jun 2020].
36 Pocock SJ, Stone GW. The primary outcome fails — what next? *N Engl J Med Overseas Ed* 2016;375:861–70.
37 Smolen JS, Burmester G-R, Combe B, *et al*. Head-To-Head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. *Lancet* 2016;388:2763–74.
38 Weinblatt ME, Schiff M, Valente R, *et al*. Head-To-Head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIB, multinational, prospective, randomized study. *Arthritis Rheum* 2013;65:28–38.
39 McInnes IB, Behrens F, Mease PJ, *et al*. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. *Lancet* 2020;395:1496–505.

CLINICAL SCIENCE

Anterior uveitis in patients with spondyloarthritis treated with secukinumab or tumour necrosis factor inhibitors in routine care: does the choice of biological therapy matter?

Ulf Lindström ,[1] Karin Bengtsson ,[1] Tor Olofsson ,[2] Daniela Di Giuseppe,[3] Bente Glintborg ,[4,5] Helena Forsblad-d'Elia,[1] Lennart T H Jacobsson,[1] Johan Askling [3]

Handling editor Josef S Smolen

► Additional online supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220420).

For numbered affiliations see end of article.

Correspondence to
Dr Ulf Lindström, Department of Rheumatology and Inflammation Research, University of Gothenburg Sahlgrenska Academy, 405 30 Gothenburg, Sweden; ulf.lindstrom@gu.se

Received 23 March 2021
Accepted 5 June 2021
Published Online First 15 June 2021

ABSTRACT

Background The effect of interleukin 17-inhibitors on anterior uveitis (AU) in spondyloarthritis (SpA) is poorly understood. This study aimed to compare the risk of AU during treatment with secukinumab versus tumour necrosis factor inhibitors (TNFi).

Methods Patients with SpA starting secukinumab or a TNFi 2015 through 2018 were identified in the Swedish Rheumatology Quality Register. Occurrence of AU was identified based on diagnosis codes in outpatient ophthalmology care in the National Patient Register. The main outcomes were crude rates of AU-diagnoses per 100 patient-years, and adjusted HRs for AU, during treatment, in patients without AU during the year before treatment start (in order to reduce confounding by indication). HRs were adjusted for age, sex, history of AU and patient global assessment of disease activity.

Results Based on 4851 treatment starts (456 secukinumab; 4395 any TNFi), the rate of AU-diagnoses per 100 patient-years was 6.8 (95% CI 5.2 to 8.7) for secukinumab. Among the TNFi, the rate varied from 2.9 (95% CI 2.1 to 3.7) for infliximab and 4.0 (95% CI 3.3 to 4.9) for adalimumab to 7.5 (95% CI 6.7 to 8.4) for etanercept. The adjusted HRs for first AU (adalimumab as reference) were: secukinumab 2.32 (95% CI 1.16 to 4.63), infliximab 0.99 (95% CI 0.49 to 1.96), etanercept 1.82 (95% CI 1.13 to 2.93), golimumab 1.59 (95% CI 0.90 to 2.80) and certolizumab 1.12 (95% CI 0.44 to 2.83). Sensitivity analyses confirmed the pattern of higher AU rates with secukinumab and etanercept versus monoclonal TNFi.

Conclusion As used in clinical practice in SpA, secukinumab appears to be associated with a higher risk of AU, compared with the monoclonal TNFi and a similar risk compared with etanercept.

Key messages

What is already known about this subject?
- Tumour necrosis factor (TNF)-inhibitors protect against anterior uveitis flares in spondyloarthritis, with a more prominent protective effect of monoclonal TNF-inhibitors compared with etanercept.
- By contrast, the effect of interleukin-17 inhibitors on anterior uveitis is poorly understood.

What does this study add?
- In this nationwide observational cohort of patients with spondyloarthritis, monoclonal TNF inhibitors were more effective, compared with secukinumab and etanercept, in protecting against anterior uveitis.

How might this impact on clinical practice or future developments?
- In patients with spondyloarthritis, monoclonal TNF-inhibitors may offer better protection against recurrent flares of anterior uveitis, compared with secukinumab and etanercept.

INTRODUCTION

Among patients with spondyloarthritis (SpA), extra-articular manifestations are frequent. A recent meta-analysis reported that 18% of patients with radiographic axial SpA (axSpA) and 14% of patients with non-radiographic axSpA (nr-axSpA) had a history of anterior uveitis (AU), and that 7% and 6%, respectively, had a history of inflammatory bowel disease (IBD), while the frequency of psoriasis was 9% in both groups.[1]

Randomised controlled trials (RCTs) of treatment of axSpA typically focus on axial disease activity,[2–4] where the effect appears to be similar across the different tumour necrosis factor inhibitors (TNFi).[5] For secukinumab and ixekizumab, indirect comparison of the results from their pivotal RCTs, together with a large observational study,[6] suggest that the effect of interleukin 17-inhibitors (IL-17i) on axial disease is in line with that of TNFi.[2 3 7]

Whereas the effects on axial disease may be similar, the effects on other SpA manifestations seem to vary substantially. In general, IL-17i are more effective than TNFi in psoriasis,[8] and while monoclonal TNFi are effective in IBD,[9 10] the soluble TNF-receptor etanercept[11] and IL-17i are not.[12 13] For IBD, the initial RCTs even suggested aggravated disease after treatment with IL-17i.[12 13] Further, although IL12/23 inhibition (ustekinumab) is effective in psoriasis,[14] psoriatic arthritis[15] and IBD,[16] it appears to lack effect on

To cite: Lindström U, Bengtsson K, Olofsson T, *et al*. *Ann Rheum Dis* 2021;**80**:1445–1452.

the axial component of axSpA,[17] highlighting the fact that the experience from TNFi cannot be uniformly extrapolated to inhibition of the IL-23/IL-17 axis.

For AU, TNFi reduces the frequency of flares in axSpA,[18 19] and the presence of AU has been linked to a better TNFi treatment retention,[20] but the protective effects regarding AU seem to be less for etanercept than for monoclonal TNFi.[19 21–24] Further, TNFi are effective in a wide range of other forms of uveitis,[25] while subcutaneous secukinumab is ineffective in non-SpA uveitis.[26] Based on currently available data, the 2019 American College of Rheumatology recommendations for management of axSpA therefore stress the need for more evidence regarding the role of IL-17i in the treatment of axSpA patients with AU.[27]

The objective of this nationwide study was to compare the risk of AU in patients with SpA treated with secukinumab or TNFi, in routine clinical care.

METHODS

Study design

Retrospective observational study on patients with SpA treated with secukinumab or TNFi in Sweden, based on prospectively collected national register data.

Data sources

Data linked through personal identification numbers, from four national registers in Sweden, were used: (1) The Swedish Rheumatology Quality register (SRQ), which prospectively collects data from routine rheumatology care, with a national coverage for biological disease-modifying antirheumatic drugs (bDMARDs) in SpA of almost 90%.[28] (2) The National Outpatient Register, collecting data from visits in outpatient specialised care since 2001. The coverage of the outpatient register is virtually complete for public specialised care, while some private care providers have incomplete reporting. In 2015–2018, 33%–39% of outpatient visits in specialised ophthalmology care were in private care.[29] (3) The Prescribed Drug Register, collecting complete patient-level data on prescribed drugs since 2005, at the time they are collected from a pharmacy.[30] (4) The Population Register, recording demographic data. All codes used to identify patients, outcomes and treatments are presented in online supplemental table S1.

Patients and treatments (exposure)

All patients with a diagnosis of ankylosing spondylitis (AS) or undifferentiated SpA (uSpA) in the SRQ, starting secukinumab or a TNFi (adalimumab, certolizumab, etanercept, golimumab or infliximab) between 1 Jan 2015 (secukinumab was introduced in 2015) and 31 December 2018 were identified. Each patient could contribute several treatment cohorts. This group is henceforth denoted 'overall cohort'.

In order to reduce the effect of confounding by indication, caused by channelling of patients with prior AU towards monoclonal TNFi, patients with an AU-diagnosis during the year prior to treatment start were then excluded, forming the 'main cohort' of the study.

Among the patients, a history of IBD was defined by >1 prior registered diagnosis of IBD in a department of gastroenterology or internal medicine. Similarly, psoriasis was defined by >1 prior diagnosis of psoriasis in dermatology care, or by a prior prescription for a psoriasis medication (to account for patients treated in primary care).

Follow-up

Follow-up for each treatment started at the date of treatment initiation, and ended at the first of: discontinuation of the treatment, end of study 31 December 2018, death or emigration.

AU (outcome)

All analyses of the primary and secondary outcomes are based on the 'main cohort', excluding patients with a diagnosis of AU in the year prior to treatment start.

The primary outcome was the rate of AU-diagnoses in outpatient ophthalmology care (based on the total number of all registered AU-diagnoses for each patient), per 100 patient-years, during the respective treatment. Each individual thus contributed with all his or her registered AU-diagnoses during the follow-up.

In addition, we constructed two AU-flare definitions, as previously described[24] : Flare definition 1—all registered visits with an AU-diagnosis separated by a gap of at least 90 days without any AU-diagnosis; Flare definition 2—all registered visits with an AU-diagnosis occurring at least 60 days after a previous registration (irrespective of any visits in-between).

The secondary outcome was the risk of a first registered AU-diagnosis in outpatient ophthalmology care during follow-up, assessed as HRs for each treatment in comparison to adalimumab (reference).

Statistical analyses

The rates for AU in the 'main cohort' were calculated per 100 patient-years, with 95% CI, using Poisson regression accounting for multiple events per individual.

HRs for risk of having a first registered AU-diagnosis during the respective treatment (in the 'main cohort') were determined through Cox regression with adalimumab as reference, crude and adjusted for age, sex, history of AU (yes/no) and patient global assessment of disease activity (quartiles and a missing category) at treatment start, including a robust sandwich estimate for the SEs to account for cases contributing more than one line of treatment. The variables were included on the basis of their potential role as confounders, where patient global assessment was chosen as a marker of disease activity, instead of the Bath Ankylosing Spondylitis Disease Activity Index or the Ankylosing Spondylitis Disease Activity Score, due to a higher proportion of missing data for the latter (table 1). The univariable association between hypothesised confounders and risk of AU are presented in online supplemental table S2. The assumption of proportional hazards was assessed through visual inspection of survival curves and through insertion of an interaction term with time in the models.

All statistical analyses were performed in SAS (V.9.4), and values of $p<0.05$ were considered statistically significant.

Sensitivity analyses

In order to further accommodate for confounding by indication, two sensitivity analyses were performed. The first analysis included all SpA patients who started treatment with adalimumab in 2004–2018 and who later stopped this treatment and within 1 year of discontinuation started secukinumab or one of the other TNFi. In this patient population the relative risk of AU on the subsequent treatments vs that on adalimumab were calculated, based on rate ratios for the rate of AU (as described for the primary outcome). The rate ratios were calculated through Poisson regression accounting for each individual contributing two consecutive treatment lines.

In the second sensitivity analysis, patients treated with secukinumab, adalimumab, golimumab or certolizumab in 2015–2018

Table 1 Baseline characteristics of patients starting secukinumab or a TNFi

	Secukinumab	Adalimumab	Etanercept	Infliximab	Golimumab	Certolizumab	Total
Treatment starts, n	**456**	**1006**	**1800**	**783**	**500**	**306**	**4851**
Sex, men, n (%)	190 (42)	507 (50)	909 (51)	405 (52)	289 (58)	124 (41)	2424 (50)
Age, years, mean (SD)	48 (13)	44 (14)	43 (14)	43 (14)	43 (14)	44 (14)	44 (14)
Diagnosis, AS n (%)	188 (41)	413 (41)	704 (39)	366 (47)	258 (52)	120 (39)	2049 (42)
BASDAI, mean (SD)	6.4 (2.0)	5.5 (2.1)	5.5 (2.0)	5.8 (2.0)	5.3 (2.3)	5.9 (2.1)	5.6 (2.1)
Missing n (%)	248 (54)	622 (62)	1053 (59)	462 (59)	283 (57)	190 (62)	2858 (59)
ASDAS, mean (SD)	3.4 (1.0)	3.0 (1.0)	3.0 (0.9)	3.2 (1.0)	3.0 (1.0)	3.2 (1.0)	3.1 (1.0)
Missing n (%)	257 (56)	669 (67)	1156 (64)	486 (62)	301 (60)	197 (64)	3066 (63)
Patient global assessment, mean (SD)	67 (21)	57 (23)	58 (22)	59 (23)	56 (24)	61 (23)	59 (23)
Missing n (%)	194 (43)	500 (50)	881 (49)	391 (50)	230 (46)	142 (46)	2338 (48)
CRP, mean (SD)	11 (22)	10 (16)	10 (16)	15 (29)	11 (20)	10 (16)	11 (20)
Missing n (%)	185 (41)	462 (46)	799 (44)	329 (42)	208 (42)	120 (39)	2103 (43)
Line of bDMARD treatment							
Line 1, n (%)	35 (8)	470 (47)	1202 (67)	539 (69)	242 (48)	79 (26)	2567 (53)
Line 2, n (%)	106 (23)	347 (34)	415 (23)	100 (13)	112 (22)	96 (31)	1176 (24)
Line 3, n (%)	129 (28)	109 (11)	93 (5)	86 (11)	76 (15)	65 (21)	558 (12)
Line ≥4, n (%)	186 (41)	80 (8)	90 (5)	58 (7)	70 (14)	66 (22)	550 (11)
IBD, n (%)	16 (4)	109 (11)	45 (3)	69 (9)	28 (6)	21 (7)	288 (6)
Psoriasis, n (%)	62 (14)	70 (7)	112 (6)	44 (6)	34 (7)	34 (11)	356 (7)
Previous AU, n (%)*	63 (14)	179 (18)	204 (11)	96 (12)	88 (18)	50 (16)	680 (14)
Concomitant csDMARDs							
Methotrexate, n(%)	73 (16)	168 (17)	255 (14)	215 (27)	77 (15)	47 (15)	835 (17)
Sulfasalazine, n (%)	27 (6)	80 (8)	164 (9)	71 (9)	41 (8)	30 (10)	413 (9)
csDMARD total, n (%)	102 (22)	251 (25)	414 (23)	282 (36)	119 (24)	82 (27)	1250 (26)

The table presents the data for the 'main cohort', excluding cases with a diagnosis of AU in the year prior to treatment start. Data were complete unless otherwise presented.
*Any registration of AU in outpatient ophthalmology care since start of the outpatient register in 2001.
AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; AU, anterior uveitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease modifying anti-rheumatic drug; CRP, C reactive protein; csDMARD, conventional synthetic DMARD; IBD, inflammatory bowel disease; TNFi, tumour necrosis factor inhibitors.

were matched, 1:1 through propensity scores, with patients treated with etanercept (constituting the largest cohort to draw comparators from). The propensity scores were based on age, sex, line of treatment and history of AU (categorised, see online supplemental table S2), using a greedy match within a calliper of 0.2 SD of the logit of the propensity score, and trimming at the 2.5th and 97.5th percentile. Measures of disease activity were not included in the propensity score due to the high proportion of missing data. HRs for a first AU-diagnosis during treatment were determined within each pair of drugs with etanercept as reference, crude and adjusted for patient global assessment of disease activity (quartiles and a missing category) at treatment start.

Patient and public involvement

Patients were not involved in the planning or execution of the study.

RESULTS

In total, 3616 patients (53% men) contributed 4851 treatment starts in the 'main cohort' in 2015–2018. There was a trend towards higher disease activity at treatment start for secukinumab compared with the TNFi, and a higher proportion of patients with psoriasis in the secukinumab group (14% vs 6%–11% for TNFi), see table 1. IBD was less frequent among those starting secukinumab (4%) and etanercept (3%) compared with the other TNFi (in particular adalimumab, 11%) and conventional synthetic DMARDs were more commonly used together with infliximab compared with the other treatments. The majority of patients initiating a TNFi started it as their first or second bDMARD, while for secukinumab 69% had used at least two previous TNFi (table 1).

Occurrence of AU

Among all patients (overall cohort), regardless of AU occurrence in the year prior to treatment start, 21% had a history of AU during the past 10 years (lower part of table 2). For secukinumab this was 18%, and for adalimumab and etanercept 32% and 14%, respectively, suggesting that the choice of treatment was influenced by previous AU history.

Excluding patients with an AU-diagnosis in the year prior to treatment start (main cohort) resulted in less pronounced differences across treatments in terms of history of AU-diagnoses during the past 10 years (secukinumab 11% vs adalimumab 15%) (top part of table 2).

New-onset AU during treatment (occurrence of an AU-diagnosis in patients with no previous registration of such diagnosis in the outpatient ophthalmology register since 2001), occurred in only 1% of patients (0.8% in previously bio-naïve) (table 2). There were numerical differences in new-onset AU among the drugs, with adalimumab being the lowest at 0.5%, and secukinumab (1.3%), certolizumab (1.6%) and etanercept (1.2%) the highest, but with frequencies too low to draw any solid conclusions (table 2).

Primary outcome: incidence rates of AU

The rates for AU per 100 patient years are presented in figure 1. Etanercept, secukinumab and golimumab displayed higher rates (with non-overlapping CIs) compared with infliximab and adalimumab, for the rate of AU based on the total number of

Table 2 Occurrence of AU before and during treatment

Treatment	AU-diagnosis prior to treatment start		Patients with ≥1 AU-diagnosis during treatment			Follow-up days, mean
	Within 10 years	Within 1 year	All	New onset*	New onset* biologics-naïve†	
Main cohort: excluding patients with an AU-diagnosis in year prior to treatment start						
Secukinumab n=456, n (%)	52 (11)	0	13 (2.9)	5 (1.3)	1 (3.3)	367
Adalimumab n=1006, n (%)	154 (15)	0	25 (2.5)	4 (0.5)	2 (0.5)	485
Infliximab n=783, n (%)	80 (10	0	13 (1.7)	4 (0.6)	2 (0.4)	473
Etanercept n=1800, n (%)	171 (10)	0	52 (2.9)	19 (1.2)	9 (0.8)	454
Golimumab n=500, n (%)	73 (15)	0	22 (4.4)	5 (1.2)	4 (1.9)	689
Certolizumab n=306, n (%)	44 (14)	0	6 (2.0)	4 (1.6)	0	425
Overall cohort: all patients starting secukinumab or a TNFi in 2015–2018						
Secukinumab n=493, n (%)	89 (18)	37 (8)	31 (6)	5 (1.3)	1 (3.3)	380
Adalimumab n=1249, n (%)	397 (32)	243 (19)	143 (11)	4 (0.5)	2 (0.5)	490
Infliximab n=883, n (%)	180 (20)	100 (11)	54 (6)	4 (0.6)	2 (0.4)	473
Etanercept n=1898, n (%)	269 (14)	98 (5)	104 (5)	19 (1.2)	9 (0.8)	459
Golimumab n=562, n (%)	135 (24)	62 (11)	56 (10)	5 (1.2)	4 (1.9)	694
Certolizumab n=335, n (%)	73 (22)	29 (9)	25 (7)	4 (1.6)	0	420

*New-onset AU=AU-diagnosis registered during treatment in patients with no AU-diagnosis prior to treatment start (the denominator is the number of patients starting the respective treatment having no prior registration of AU since start of outpatient register in 2001).
†Previously biologics-naïve patients.
AU, anterior uveitis; TNFi, tumour necrosis factor inhibitors.

registered AU-diagnoses, and with varying degree of statistical significance for the two flare definitions. Details on number of AU-diagnoses/flares and follow-up times are presented in online supplemental table S3.

Secondary outcome: HRs of AU

The adjusted HRs for a first AU during follow-up indicated significantly higher risks for secukinumab (HR: 2.32; 95% CI 1.16 to 4.63) and etanercept (HR: 1.82; 95% CI 1.13 to 2.93), compared with adalimumab (reference); results for the other TNFi are presented in table 3. No evidence of non-proportionality was found.

Sensitivity analysis

In total, 1119 patients were included in the analysis comparing rate ratios of AU between a subsequent bDMARD treatment and a previous treatment with adalimumab. Of these, 74 patients were subsequently treated with secukinumab, 200 with infliximab, 516 with etanercept, 217 with golimumab and 112 with certolizumab (see online supplemental table S4). The rate ratios

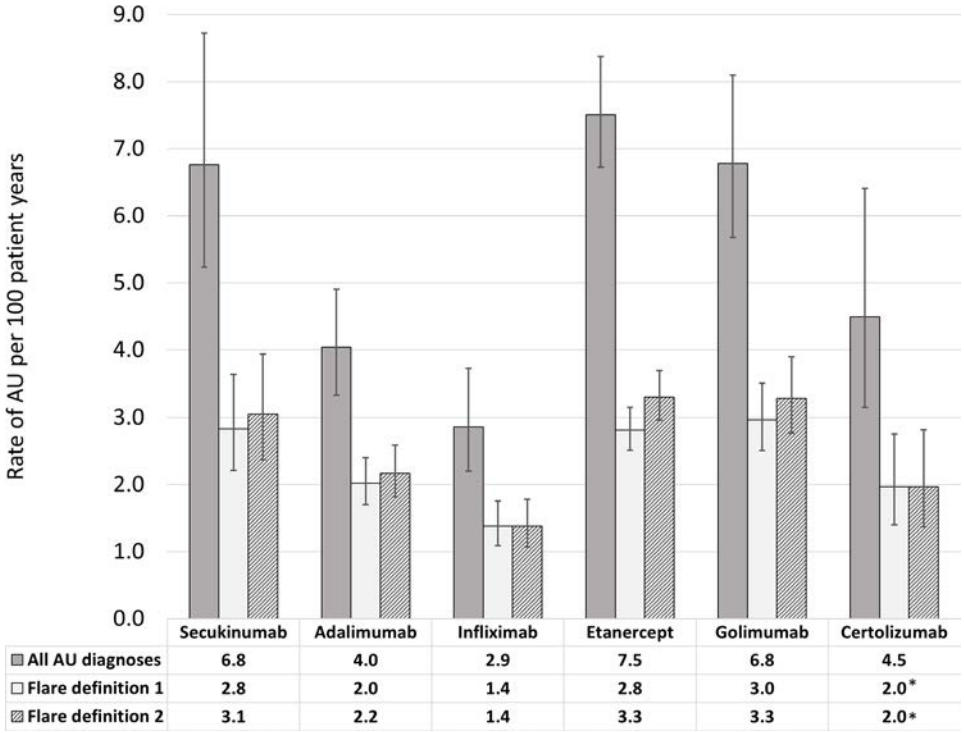


Figure 1 Rate of anterior uveitis (AU) per 100 patient-years during treatment. Error bars indicate 95% CI. *Rate based on <10 events, see online supplemental table S3. Flare definition 1: all registered visits with an AU-diagnosis separated by a gap of at least 90 days without any AU -diagnosis; flare definition 2: all registered visits with an AU-diagnosis occurring at least 60 days after a previous registration (irrespective of any visits in-between).

Table 3 HR of first on-treatment AU

	N with AU event/N total	Crude HR	Adjusted HR*
Adalimumab	25/1006	Ref	Ref
Secukinumab	13/456	1.53 (0.78–3.02)	2.32 (1.16–4.63)
Etanercept	52/1800	1.25 (0.77–2.01)	1.82 (1.13–2.93)
Infliximab	13/783	0.68 (0.35–1.32)	0.99 (0.49–1.96)
Golimumab	22/500	1.25 (0.71–2.21)	1.59 (0.90–2.80)
Certolizumab	6/306	0.90 (0.37–2.19)	1.12 (0.44–2.83)

*Adjusted for sex, age, previous history of AU and patient global assessment.
AU, anterior uveitis.

are shown in figure 2. Irrespective of AU definition, the rates were significantly higher after (vs before) switching from adalimumab to secukinumab, etanercept or certolizumab, but not after switching to infliximab or golimumab.

The propensity score matched pairs are presented in table 4. The pairs were well matched with regard to history of AU and line of treatment, but with some within-pair differences observed for disease activity (see online supplemental table S5 for standardised differences in the matched pairs). The crude and adjusted HR indicated a lower risk for AU on adalimumab, infliximab, golimumab and certolizumab (not statistically significant) compared with etanercept, but a similar risk for secukinumab.

DISCUSSION

In this nationwide observational study of SpA in clinical practice, treatment with adalimumab and infliximab were associated with a lower risk for AU compared with secukinumab and etanercept, but new-onset AU (in patient without previous AU) was very rare regardless of treatment. For certolizumab and golimumab the direction of the results was not consistent, and the higher crude

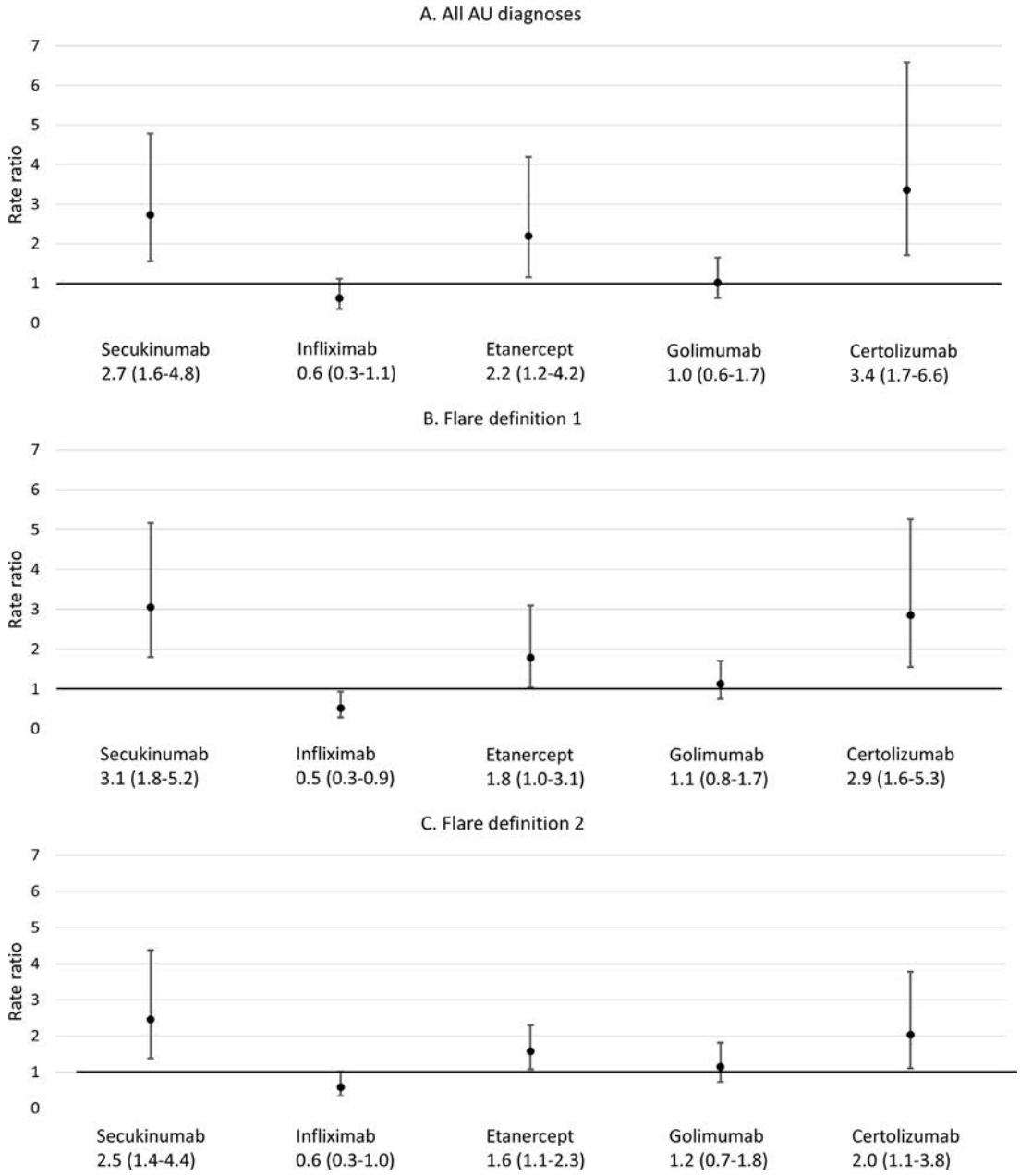


Figure 2 Rate ratios for anterior uveitis (AU), comparing each treatment with a prior adalimumab treatment. Flare definition 1: all registered visits with an AU-diagnosis separated by a gap of at least 90 days without any AU-diagnosis; flare definition 2: all registered visits with an AU-diagnosis occurring at least 60 days after a previous registration (irrespective of any visits in-between).

Table 4 Demographics and HR in propensity score matched analysis

	SEC versus ETN		ADA versus ETN		IFX versus ETN		GOL versus ETN		CER versus ETN	
N	251:251		826:826		745:745		473:473		240:240	
Line, mean (SD)	2.7 (1.0)	2.7 (1.0)	1.6 (1.0)	1.6 (1.0)	1.5 (1.1)	1.5 (1.0)	1.7 (1.0)	1.6 (0.9)	2.0 (1.0)	2.0 (1.0)
Age, mean (SD)	47 (13)	46 (13)	44 (13)	45 (13)	43 (14)	43 (14)	42 (14)	42 (13)	43 (14)	42 (12)
Sex, n (%) men	111 (44)	104 (41)	446 (54)	447 (54)	401 (54)	393 (53)	274 (58)	283 (60)	109 (45)	110 (46)
AU ever*, n (%)	47 (19)	52 (21)	217 (26)	211 (26)	138 (19)	150 (20)	119 (25)	128 (27)	54 (23)	58 (24)
AU 1 year 2, n (%)	19 (8)	20 (8)	79 (10)	74 (9)	59 (8)	58 (8)	48 (12)	55 (10)	24 (10)	24 (10)
Patient global assessment, mean (SD)	65 (22)	59 (24)	55 (24)	58 (23)	58 (24)	59 (23)	54 (25)	57 (21)	59 (24)	58 (23)
BASDAI, mean (SD)	6.2 (2.1)	5.5 (2.1)	5.3 (2.2)	5.5 (2.1)	5.6 (2.0)	5.5 (2.0)	5.1 (2.3)	5.4 (1.9)	5.8 (2.2)	5.7 (2.1)
AU events‡	18	20	55	79	35	60	42	42	19	19
HR AU-diagnosis	1.56 (0.80–3.05)	Ref	0.56 (0.40–0.78)	Ref	0.50 (0.34–0.73)	Ref	0.55 (0.36–0.85)	Ref	0.80 (0.39–1.67)	Ref
HR AU-diagnosis Adjusted§	1.59 (0.79–3.18)	Ref	0.55 (0.39–0.78)	Ref	0.50 (0.34–0.73)	Ref	0.53 (0.34–0.81)	Ref	0.79 (0.38–1.64)	Ref

The propensity scores were based on, age, sex, line of treatment and prior AU history, see the Methods section.
*Any registration of AU prior to treatment start.
†Any registration of AU in year prior to treatment start.
‡Number of patients with an event (=first AU-diagnosis) during follow-up.
§Adjusted for patient global assessment.
ADA, adalimumab; AU, anterior uveitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CER, certolizumab; ETN, etanercept; GOL, golimumab; IFX, infliximab; SEC, secukinumab.

rates could be biased. However, in the sensitivity analyses, golimumab performed in a similar way as the other two monoclonal TNFi in both analyses, while certolizumab was associated with a lower risk of AU compared with etanercept in one analysis. The other available IL-17i, ixekizumab, was not assessed in this study.

A better understanding of the performance of IL-17i in AU is important for the positioning of the treatment in SpA treatment recommendations. An early proof-of-concept study suggested a beneficial effect of intravenous secukinumab in non-infectious uveitis.[31] However, out of three subsequent RCTs investigating standard subcutaneous secukinumab in non-infectious uveitis, one failed to show a difference in efficacy compared with placebo, another was terminated due to lack of efficacy in interim analyses, and the last one terminated due to the results in the former two.[26] To determine if higher intravenous doses were more effective than subcutaneous doses, another small (N=37) trial compared 300 mg secukinumab subcutaneously every 2 weeks, with 10 mg/kg intravenously every 2 weeks, and 30 mg/kg intravenously every 4 weeks.[32] In that study, response rates were better for the intravenous high dose regimens. In the RCTs of AS, for both secukinumab[3] and ixekizumab[33 34] there were numerically more patients experiencing AU in the active treatment groups, although the frequencies were low. In the nr-axSpA RCTs the rates were similar in active treatment and placebo groups.[35 36] In a post hoc analysis of pooled data from the AS RCTs for secukinumab, including up to 4 years of treatment with secukinumab, 1.5% of the patients experienced a new-onset AU.[37] This is well in accordance with the 1.3% of secukinumab-treated patients in our study with a new-onset AU, also here with up to 4 years of follow-up.

When comparing AU incidence across studies, it is crucial to consider the proportion of patients with a history of AU, since previous AU is a strong risk factor for new AU flares (online supplemental table S2). For example, in one study the incidence of AU flares on adalimumab was 14 per 100 patient-years, with 43% having a prior history of AU,[38] while another study reports an on-adalimumab rate of 7.4, with 22% having a history of AU.[18] AU rates during treatment with golimumab was assessed in the GO-EASY study, where the flare rate was 2.2 per 100 patient-years, in AS patients of which 27% had a history of AU.[39] In our study, actively excluding patient with AU in the last year, 18% of the golimumab-treated patients had a history of AU, while we found flare rates at 3 per 100 patient-years. This might indicate that our flare definitions are more comprehensive and add additional precision, although overestimation is also a possibility. Whatever the reason, the higher flare rate seen here would not be expected to bias our comparisons across the different DMARDs. The effect of certolizumab on AU in axSpA has been published as interim results from the C-VIEW trial.[40] In that study, patients with at least one flare in the last year (ie, highly prone to develop new flares), were treated with certolizumab. The results indicated a significant reduction in AU-flares, with an on-treatment rate of 19 per 100 patient-years. The heterogeneity introduced by different study populations having different pretreatment risk of AU, makes indirect comparison across studies very difficult, and stresses the need for direct comparisons, as performed in our study.

Several limitations should be acknowledged. First, despite our efforts to reduce the impact of confounding by indication, residual confounding is likely to occur. Second, although we included a large number of patients, some of the subset analyses were presumably underpowered and especially for certolizumab the AU rates should be interpreted with caution due to few events. Third, AU-diagnoses in the register might not

be a sufficient measure of AU-flares. However, the number of registered AU-diagnoses overall should constitute an unbiased measure of AU burden/severity, and the two AU-flare definitions used may alleviate this limitation. Fourth, since the registrations in the SRQ are based on the International Classification of Diseases (ICD)-10 codes, nr-axSpA cannot be adequately discerned. Therefore AS and uSpA (including both nr-axSpA and peripheral SpA) were included instead, bearing in mind the different prevalence of AU.[41 42]

Fifth, since a comparable SpA population not treated with bDMARDs could not readily be identified in either of the data sources included in the study, a comparison with untreated patients was not possible. This precludes the possibility to discern if secukinumab is neutral (vs bDMARD-naïve SpA) in terms of risk for AU, is associated with an increased risk of AU, or if it has a protective effect of a relatively lower magnitude compared with the monoclonal TNFi. However, the very low rates of new onset AU on either of the bDMARDs would suggest the latter to be true.

Sixth, AU among patients seeking private ophthalmology healthcare (among which the reporting to the Patient Register may be lower than for public care providers) may not have been captured in this study. It is unlikely that this would bias our results, due to the general availability of subsidised healthcare in Sweden, although it cannot be ruled out that utilisation of private healthcare and level of health literacy may correlate with treatment choice and intensity for both SpA and AU.

Finally, misclassification is always present in register-based studies, but there is no reason to suspect that this would have introduced a bias with regard to bDMARD type.

This study also has strengths. To our knowledge, it is the first report comparing the occurrence of AU in a SpA population across the five TNFi and an IL17i, when used according to clinical routine. Furthermore, we have used several different approaches to minimise confounding by indication.

To conclude, regardless of type of TNFi or secukinumab, new-onset AU is rare during biological treatment. Furthermore, the monoclonal TNFi appear to be more effective choices for preventing AU in SpA patients, compared with etanercept and secukinumab.

Author affiliations
[1]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[2]Department of Clinical Sciences Lund, Rheumatology, Lund University, Lund, Sweden
[3]Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden
[4]DANBIO and Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre of Head and Orthopedics, Rigshospitalet, Copenhagen, Denmark
[5]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Contributors All authors have contributed substantially according to the contributorship guidelines.

Funding The study was financed by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement, and by grants from Nordforsk, Foreum and the Swedish Research Council.

Competing interests TO reports personal fees from Eli Lilly, other from Merck Sharp & Dohme, outside the submitted work. BG reports grants from BMS, grants from Pfizer, grants from AbbVie, outside the submitted work. LTJ reports personal fees from Novartis, personal fees from Eli-Lily, personal fees from Janssen, outside the submitted work. JA reports grants from Abbvie, Astra-Zeneca, BMS, Eli Lilly, MSD, Pfizer, Roche, Samsung Bioepis, Sanofi, and UCB, outside the submitted work. The remaining authors have nothing to disclose.

Patient consent for publication Not required.

Ethics approval The ethical review board in Stockholm, Sweden, approved the study (dnr:2011/29-31/1 and 2015-1844-31/2). Informed consent was not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

ORCID iDs
Ulf Lindström http://orcid.org/0000-0002-2250-9348
Karin Bengtsson http://orcid.org/0000-0001-5154-0144
Tor Olofsson http://orcid.org/0000-0002-9919-4487
Bente Glintborg http://orcid.org/0000-0002-8931-8482
Johan Askling http://orcid.org/0000-0003-0433-0616

REFERENCES

1 López-Medina C, Ramiro S, van der Heijde D, *et al*. Characteristics and burden of disease in patients with radiographic and non-radiographic axial spondyloarthritis: a comparison by systematic literature review and meta-analysis. *RMD Open* 2019;5:e001108.
2 van der Heijde D, Kivitz A, Schiff MH, *et al*. 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.
3 Baeten D, Sieper J, Braun J, *et al*. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. *N Engl J Med* 2015;373:2534–48.
4 Inman RD, Davis JC, Heijde Dvander, Heijde DVD, *et al*. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum* 2008;58:3402–12.
5 Maxwell LJ, Zochling J, Boonen A, *et al*. Tnf-alpha inhibitors for ankylosing spondylitis. *Cochrane Database Syst Rev* 2015;53:Cd005468.
6 Glintborg B, Lindstrom U, Di Giuseppe D, *et al*. One-Year treatment outcomes of secukinumab versus tumor necrosis factor inhibitors in spondyloarthritis. *Arthritis Care Res* 2020. doi:10.1002/acr.24523. [Epub ahead of print: 30 Nov 2020].
7 Sieper J, van der Heijde D, Dougados M, *et al*. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis* 2013;72:815–22.
8 Sbidian E, Chaimani A, Garcia-Doval I, *et al*. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev* 2017;42:Cd011535.
9 Hanauer SB, Sandborn WJ, Rutgeerts P, *et al*. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006;130:323–33.
10 Rutgeerts P, Sandborn WJ, Feagan BG, *et al*. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353:2462–76.
11 Sandborn WJ, Hanauer SB, Katz S, *et al*. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2001;121:1088–94.
12 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.
13 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.
14 Leonardi CL, Kimball AB, Papp KA, *et al*. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (Phoenix 1). *Lancet* 2008;371:1665–74.
15 Ritchlin C, Rahman P, Kavanaugh A, *et al*. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis* 2014;73:990–9.

16 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.
17 Deodhar A, Gensler LS, Sieper J, *et al*. Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. *Arthritis Rheumatol* 2019;71:258–70.
18 Rudwaleit M, Rødevand E, Holck P, *et al*. Adalimumab effectively reduces the rate of anterior uveitis flares in patients with active ankylosing spondylitis: results of a prospective open-label study. *Ann Rheum Dis* 2009;68:696–701.
19 Braun J, Baraliakos X, Listing J, *et al*. Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. *Arthritis Rheum* 2005;52:2447–51.
20 Lindström U, Olofsson T, Wedrén S, *et al*. Impact of extra-articular spondyloarthritis manifestations and comorbidities on drug retention of a first TNF-inhibitor in ankylosing spondylitis: a population-based nationwide study. *RMD Open* 2018;4:e000762.
21 Wendling D, Joshi A, Reilly P, *et al*. Comparing the risk of developing uveitis in patients initiating anti-tumor necrosis factor therapy for ankylosing spondylitis: an analysis of a large US claims database. *Curr Med Res Opin* 2014;30:2515–21.
22 Wendling D, Paccou J, Berthelot J-M, *et al*. New onset of uveitis during anti-tumor necrosis factor treatment for rheumatic diseases. *Semin Arthritis Rheum* 2011;41:503–10.
23 Guignard S, Gossec L, Salliot C, *et al*. Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study. *Ann Rheum Dis* 2006;65:1631–4.
24 Lie E, Lindström U, Zverkova-Sandström T, *et al*. Tumour necrosis factor inhibitor treatment and occurrence of anterior uveitis in ankylosing spondylitis: results from the Swedish biologics register. *Ann Rheum Dis* 2017;76:1515–21.
25 Jaffe GJ, Dick AD, Brézin AP, *et al*. Adalimumab in patients with active noninfectious uveitis. *N Engl J Med* 2016;375:932–43.
26 Dick AD, Tugal-Tutkun I, Foster S, *et al*. Secukinumab in the treatment of noninfectious uveitis: results of three randomized, controlled clinical trials. *Ophthalmology* 2013;120:777–87.
27 Ward MM, Deodhar A, Gensler LS, *et al*. 2019 update of the American College of Rheumatology/Spondylitis association of America/Spondyloarthritis research and treatment network recommendations for the treatment of ankylosing spondylitis and Nonradiographic axial spondyloarthritis. *Arthritis Care Res* 2019;71:1285–99.
28 Wadström H, Eriksson JK, Neovius M, *et al*. How good is the coverage and how accurate are exposure data in the Swedish biologics register (ARTIS)? *Scand J Rheumatol* 2015;44:22–8.
29 Verksamhetstabeller 2010-2019, 2019. Available: https://skr.se/download/18.68bc273e172cda17ad44ec48/1602684039044/Verksamhetsstatistik%202010-2019.xlsx
30 Wettermark B, Hammar N, Fored CM, MichaelFored C, *et al*. The new Swedish prescribed drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007;16:726–35.
31 Hueber W, Patel DD, Dryja T, *et al*. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. *Sci Transl Med* 2010;2:52ra72.
32 Letko E, Yeh S, Foster CS, *et al*. Efficacy and safety of intravenous secukinumab in noninfectious uveitis requiring steroid-sparing immunosuppressive therapy. *Ophthalmology* 2015;122:939–48.
33 van der Heijde D, Cheng-Chung Wei J, Dougados M, *et al*. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. *Lancet* 2018;392:2441–51.
34 Deodhar A, Poddubnyy D, Pacheco-Tena C, *et al*. Efficacy and safety of ixekizumab in the treatment of radiographic axial spondyloarthritis: sixteen-week results from a phase III randomized, double-blind, placebo-controlled trial in patients with prior inadequate response to or intolerance of tumor necrosis factor inhibitors. *Arthritis Rheumatol* 2019;71:599–611.
35 Deodhar A, Blanco R, Dokoupilová E. Secukinumab improves signs and symptoms of non-radiographic axial spondyloarthritis: primary results of a randomized controlled phase III study. *Arthritis Rheumatol* 2021;73:110–20.
36 Deodhar A, van der Heijde D, Gensler LS, *et al*. Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial. *Lancet* 2020;395:53–64.
37 Deodhar AA, Miceli-Richard C, Baraliakos X, *et al*. Incidence of uveitis in Secukinumab-treated patients with ankylosing spondylitis: pooled data analysis from three phase 3 studies. *ACR Open Rheumatol* 2020;2:294–9.
38 van Denderen JC, Visman IM, Nurmohamed MT, *et al*. Adalimumab significantly reduces the recurrence rate of anterior uveitis in patients with ankylosing spondylitis. *J Rheumatol* 2014;41:1843–8.
39 van Bentum RE, Heslinga SC, Nurmohamed MT, *et al*. Reduced occurrence rate of acute anterior uveitis in ankylosing spondylitis treated with golimumab - The GO-EASY study. *J Rheumatol* 2019;46:153–9.
40 van der Horst-Bruinsma I, van Bentum R, Verbraak FD, *et al*. The impact of certolizumab pegol treatment on the incidence of anterior uveitis flares in patients with axial spondyloarthritis: 48-week interim results from C-VIEW. *RMD Open* 2020;6:e001161.
41 Bengtsson K, Forsblad-d'Elia H, Deminger A, *et al*. Incidence of extra-articular manifestations in ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis: results from a national register-based cohort study. *Rheumatology* 2020;377. doi:10.1093/rheumatology/keaa692. [Epub ahead of print: 20 Nov 2020].
42 Lindström U, Exarchou S, Sigurdardottir V, *et al*. Validity of ankylosing spondylitis and undifferentiated spondyloarthritis diagnoses in the Swedish national patient register. *Scand J Rheumatol* 2015;44:369–76.

TRANSLATIONAL SCIENCE

Single-cell transcriptome analysis identifies skin-specific T-cell responses in systemic sclerosis

Alyxzandria M Gaydosik,[1] Tracy Tabib,[1] Robyn Domsic ,[1] Dinesh Khanna ,[2] Robert Lafyatis,[1] Patrizia Fuschiotti [1]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220209).

[1]Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[2]Division of Rheumatology, University of Michigan Medical School, Ann Arbor, Michigan, USA

Correspondence to
Dr Patrizia Fuschiotti, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA; paf23@pitt.edu

Received 20 February 2021
Accepted 8 May 2021
Published Online First 24 May 2021

ABSTRACT

Objectives Although T cells have been implicated in the pathogenesis of systemic sclerosis (SSc), a comprehensive study of T-cell-mediated immune responses in the affected skin of patients with progressive SSc is lacking. Droplet-based single-cell transcriptome analysis of SSc skin biopsies opens avenues for dissecting patient-specific T-cell heterogeneity, providing a basis for identifying novel gene expression related to functional pathways associated with severity of SSc skin disease.

Methods Single-cell RNA sequencing was performed by droplet-based sequencing (10x Genomics), focusing on 3729 $CD3^+$ lymphocytes (867 cells from normal and 2862 cells from SSc skin samples) from skin biopsies of 27 patients with active SSc and 10 healthy donors. Confocal immunofluorescence microscopy of progressive SSc skin samples validated transcriptional results and visualised spatial localisations of T-cell subsets.

Results We identified several subsets of recirculating and tissue-resident T cells in healthy and SSc skin that were associated with distinct signalling pathways. While most clusters shared a common gene expression signature between patients and controls, we identified a unique cluster of recirculating $CXCL13^+$ T cells in SSc skin which expressed a T helper follicular-like gene expression signature and that appears to be poised to promote B-cell responses within the inflamed skin of patients.

Conclusions Current available therapies to reverse or even slow progression of SSc lead to broad killing of immune cells and consequent toxicities, including death. Identifying the precise immune mechanism(s) driving SSc pathogenesis could lead to innovative therapies that selectively target the aberrant immune response, resulting in better efficacy and less toxicity.

Key messages

What is already known about this subject?

- Current available therapies to reverse or even slow progression of systemic sclerosis (SSc), such as myeloablation, lead to broad killing of immune cells and consequent toxicities, including death.
- Although T cells have been implicated in the pathogenesis of SSc, a comprehensive study of T-cell-mediated immune responses in the affected skin of patients with progressive SSc is lacking.

What does this study add?

- Our analysis provides an unprecedented view of T-cell heterogeneity in SSc skin.
- We identified a distinct $CXCL13^+$ T-cell subset that expresses factors enabling B-cell help and likely promoting B-cell responses and possibly autoantibodies production within pathological inflamed skin.

How might this impact on clinical practice or future developments?

- These results provide a better understanding of T cell responses in SSc skin disease, allowing development of more targeted T cell therapy in SSc that results in better efficacy and less toxicity, thus realising the goal of precision medicine.

INTRODUCTION

Systemic sclerosis (SSc) is a disabling and often fatal autoimmune disease characterised by vasculopathy, inflammation, and extensive cutaneous and visceral fibrosis.[1] SSc has the highest fatality rate among connective tissue diseases and few therapies are available that reverse or even slow progression. Several T-lymphocyte subsets and the cytokines they produce have been implicated in the inflammatory and fibrotic processes of SSc.[2 3] Particularly, we and others identified increased numbers of profibrotic T-cell subsets including Th2 and Tc2 cells producing interleukin (IL)-4 and IL-13[4 5] as well as IL-21-producing T follicular helper (T_{FH})-like cells[6] in the blood and in the sclerotic skin of patients with active SSc. Moreover, skin infiltrating Th17 and Th22 cells producing IL-17-family cytokines were shown to drive inflammatory responses involving fibroblasts and endothelial cells,[3] whereas IL-9 produced by Th9 cells was shown to induce NETosis, expansion of mast cells and increased production of SSc-related autoantibodies by B lymphocytes.[7] Deregulation of T regulatory (Treg) cell function was also associated with altered immune homeostasis and fibrosis in SSc.[8 9] Finally, cytotoxic $CD8^+$ and $CD4^+$ T cells[4 10] in the lesional skin of patients with early active SSc were also detected. These cells express markers of cytotoxicity and are likely involved in tissue damage and in perpetuating autoimmune responses.[11] However, a comprehensive study of resident and recirculating T-cell subpopulations in SSc skin disease remains elusive.

Recent advances in single-cell transcriptome technology, including droplet-based single-cell RNA sequencing (scRNAseq),[12] profile gene expression

To cite: Gaydosik AM, Tabib T, Domsic R, *et al*. *Ann Rheum Dis* 2021;**80**:1453–1460.

across thousands of individual cells from a large heterogeneous population such as a patient biopsy. This high-resolution analysis of cellular heterogeneity reveals individual cell functions in the context of their microenvironment and provides striking insights into the complex cellular composition of normal and diseased tissue. Here we report scRNAseq analysis of T cells from the affected skin of patients with progressive SSc. This analysis provides an unprecedented view of lymphocyte heterogeneity within the skin microenvironment of individual SSc skin sample and offers important implications for personalised disease management.

METHODS

Full-thickness 3 mm skin biopsies were obtained from 32 patients with confirmed diagnosis of active diffuse cutaneous SSc (dcSSc)[13 14] at the Scleroderma Clinic of UPMC and at the Scleroderma Programme of the University of Michigan Medical School. Disease subtype and internal organ involvement were assessed according to established criteria.[13–15] All participants gave written informed consent in accordance with the Declaration of Helsinki. Twenty-seven patient samples were used for scRNA-seq and five for immunofluorescence (IF) microscopy. Experimental procedures for scRNAseq followed established techniques using the Chromium Single Cell 3' Library V2 kit (10x Genomics).[16] Multicolour antibody staining using tyramide signal amplification (Thermo Fisher) was performed on formalin-fixed, paraffin-embedded skin samples as previously described.[17] See online supplemental methods for details. All scRNA-seq data have been deposited in the Gene Expression Omnibus: GSE138669.

RESULTS

Single-cell transcriptome profiles reveal T lymphocyte heterogeneity in dcSSc skin lesions

ScRNAseq was used to profile the transcriptome of T lymphocytes obtained from the enzymatically digested skin of 27 active dcSSc and 10 HC samples (online supplemental figure S1 and table S1). Histological evaluation of SSc skin lesions shows increased collagen deposition in the dermis, thickening of the collagen fibre bundles and subintimal thickening of blood vessels, as well as perivascular mononuclear cell infiltration compared with control skin (figure 1A). In total, we analysed 3729 $CD3^+$ cells: 867 from HC and 2862 from SSc skin (figure 1B). Comparison of the transcriptional profiles of each lymphocyte subset from the patient and control skin samples identified nine clusters (figure 1C and online supplemental table S2). In parallel to principal components analysis (PCA), Harmony[18] was used to demonstrate that the samples did not suffer from any batch effects (online supplemental figure S2). By comparing gene expression from each cell in the cluster with that of all other cells in the dataset, we determined the differential expression (DE) of genes in each cluster. The cut-off for significance was $p<0.05$ and we required that gene expression be from at least 25% of cells in the cluster. The heatmap in figure 1D reports examples of the most highly significant DE genes for each cluster. Conventional $CD4^+$ T cells comprised three clusters (#0, 1 and 4) distinguished from each other by only subtle transcriptome differences. Cluster #2 identifies $CD8^+$ T cells, while cluster #3 identifies Tregs. Cytokine *IL-26* is the signature gene of cluster #5, *CXCL13* of cluster #7 and *TRDC* of cluster #8. Cells in cluster #6 express proliferation genes. We next employed Ingenuity Pathway Analysis[19] to identify activation of key molecular pathways in each T-cell cluster (figure 1E). Examples of pathways activated in each lymphocyte cluster included IL-7 and PI3K/AKT signalling (cluster #0); glucocorticoid receptor and TNFR2 signalling (cluster #1); Th1, Th2 activation and T-cell exhaustion signalling (cluster #2); and ICOS-ICOSL and PD1-PDL1 signalling (cluster #3). Clusters #4, 6 and 7 upregulated the expression of oxidative phosphorylation and mitochondrial pathways. The ERK/MAPK signalling pathway was also upregulated by cluster #7, while clusters #5 and 8 upregulated the HMGB1 signalling pathway. Within each cluster, no consistent changes were observed in the proportion of T cells between SSc and control samples, apart from cluster #6 where we found a statistically significant increase of SSc T cells and in cluster #7 that was comprised uniquely of cells from SSc samples (figure 1F). Figure 1G demonstrates the SSc-exclusive expression of signature genes (*CXCL13*, *CD200* and *MS4A6A*) from cluster #7. Thus, scRNAseq analysis provides an unprecedented view of T lymphocyte heterogeneity in the skin lesions of patients with active dcSSc and identifies a unique subset found only in patient samples.

Cell state transition of resident and recirculating T cells in healthy and SSc skin

The tissue distribution of skin-resident and skin-recirculating T cells was established by determining expression of CD69, ITGAE, CCR7 and SELL.[20] The normalised single-cell expression showed that *CD69* was expressed by a large number of cells in most T-cell clusters, exhibiting modestly upregulated expression in SSc T cells, whereas *ITGAE* was detected in fewer cells, primarily from cluster #6 (figure 2A–B). *CCR7* and *SELL* expression also appeared to be confined to specific clusters (figure 2A–B). Specifically, *CCR7* was mainly expressed by cells in clusters #0, 6 and 7, with a higher number of $CCR7^+$ cells in SSc versus HC skin samples (figure 2B). *SELL* was primarily expressed by SSc T cells in clusters #0, 3 and 6. Although we cannot exclude the presence of cells in transitional states within each cluster, our findings indicated that T cells in clusters #1, 2, 3, 4, 5 and 8 exhibited predominantly a skin-resident phenotype (T_{RM}, $CD69^+ITGAE^{+/-}$). These included $CD4^+$, $CD8^+$ and T_{reg} populations. In contrast, most SSc T cells in clusters #0 and 7 expressed markers of recirculating memory migratory cells (T_{MM}, $CCR7^+SELL^-$), the latter representing the population most highly upregulated in SSc skin. Finally, proliferating T cells in cluster #6, also mainly present in SSc skin, represented a mix of T_{RM} and T_{MM} cells.

We performed a trajectory analysis using Monocle 3[21 22] to examine the connection between skin residency and kinetics of gene expression during $CD4^+$ and $CD8^+$ T-cell differentiation in SSc skin. This algorithm uses a concept referred to as pseudotime, in theory examining the change in phenotype of cell types over time. However, here it examines changes in gene expression, relating each cell to other cells and ordering the cells showing the closest transcriptomes adjacent to each other. It may but does not necessarily indicate a descendant–progenitor relationship. All T cells from SSc and healthy skin were placed on these trajectories based on changes in their transcriptome (figure 2C). Strikingly, both $CD4^+$ and $CD8^+$ T cells from HC samples were distributed to early pseudotimes, whereas SSc T cells were enriched in late pseudotimes, showing a clear temporal separation (figure 2D). We then examined the transition of average expression values along pseudotime for a panel of marker genes associated with T-cell residency. We found that HC $CD4^+$ and $CD8^+$ T cells exhibited a T_{RM} phenotype as these cells highly expressed *CD69* and expressed only low levels of

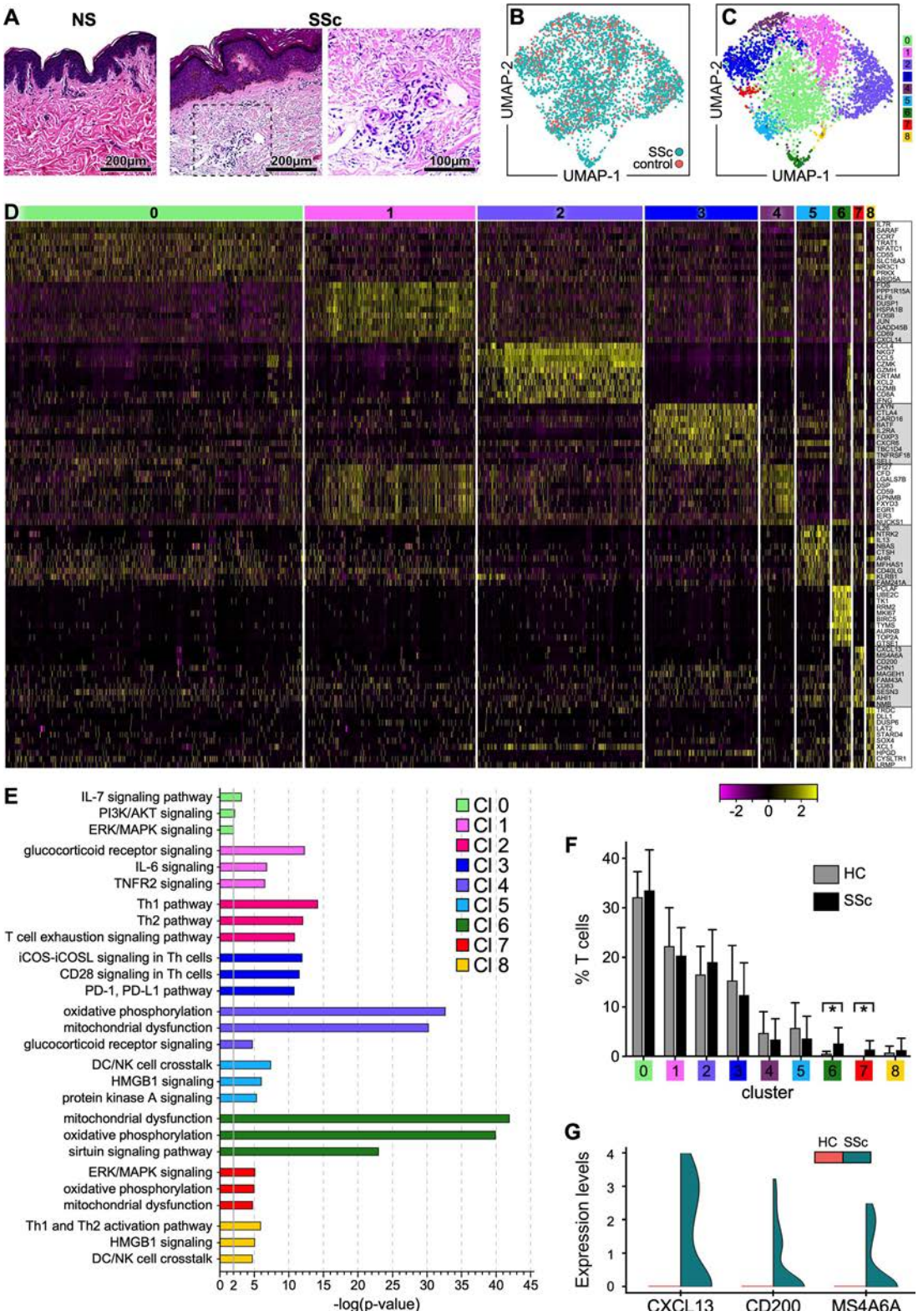


Figure 1 Transcriptional profiles of T lymphocytes from systemic sclerosis (SSc) and healthy control (HC) skin samples. (A) H&E staining of skin biopsies from representative HC and SSc skin samples analysed by scRNA-seq (×200, ×400). (B) Transcriptomes of 3729 $CD3^+$ cells (867 cells from HC and 2862 cells from SSc skin samples) (C) revealed nine discrete Louvain clusters using Seurat.[58] (D) Heatmap showing examples of the most highly significant differentially expressed genes (n=10) for each cluster from (C). Cluster numbers are indicated at the top. Each column represents a cell. (E) Pathway analysis by Ingenuity (Qiagen). Highly significant examples of distinct pathways activated in each cluster are shown. In Ingenuity Pathway Analysis, the pathways were compared using a p value cut-off of 0.05. (F) Proportion of T cells from each patient or control sample within each cluster. Statistics by Mann-Whitney test. (G) Violin plot showing the expression levels of *CXCL13*, *CD200* and *MS4A6A* by cells in cluster #7 comparing SSc with HC samples. IL-7, interleukin-7; SSc and HC UMAP, Uniform Manifold Approximation and Projection for dimension reduction.

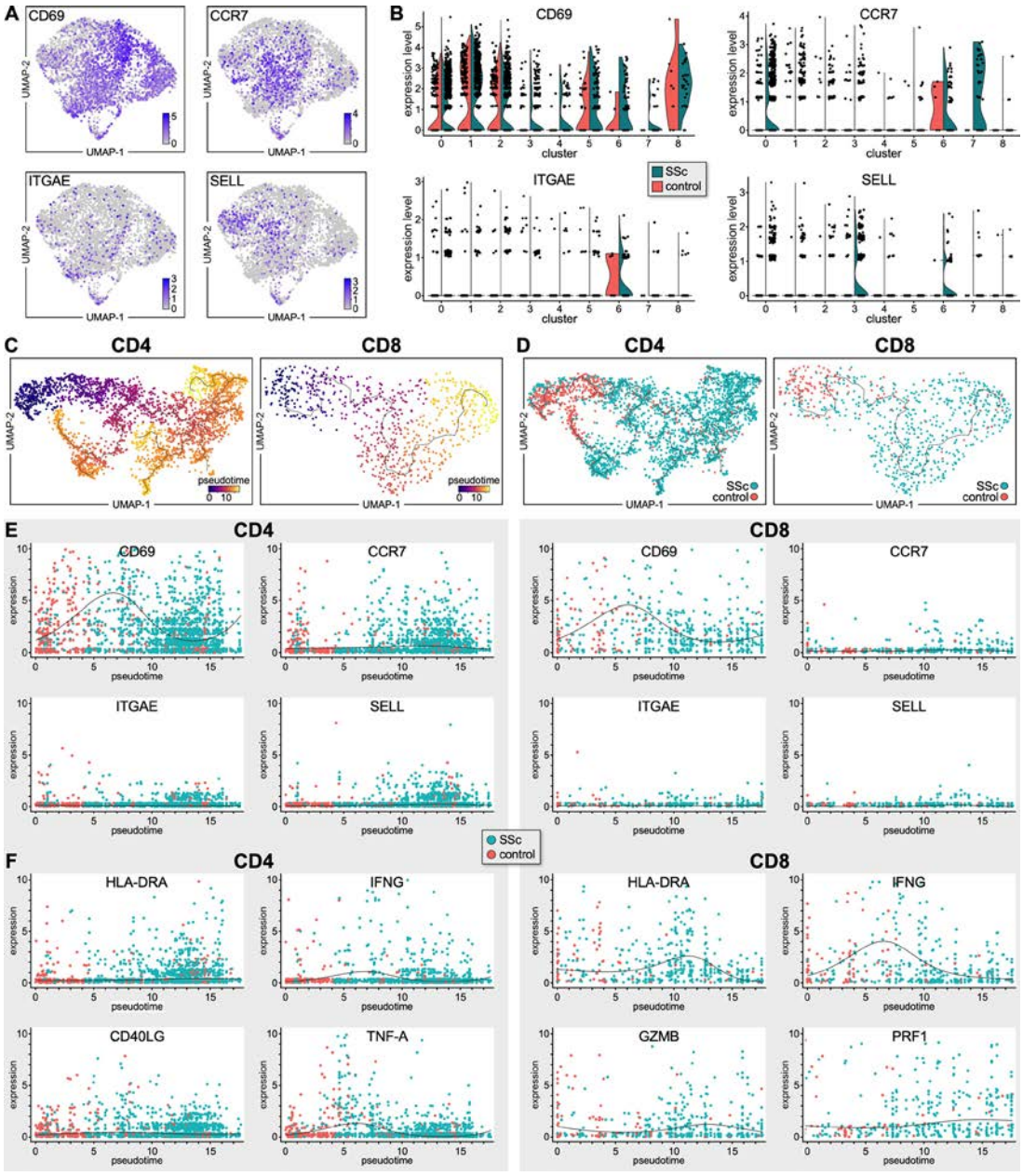


Figure 2 Identification of resident and recirculating T cells in healthy and systemic sclerosis (SSc) skin. (A) Transcriptomes of CD69$^+$, CCR7$^+$, ITGAE$^+$, SELL$^+$ T lymphocytes from patient and healthy control (HC) skin samples. (B) Violin plots showing expression levels of *CD69*, *CCR7*, *ITGAE*, *SELL* by SSc and HC T lymphocytes from each T-cell cluster (figure 1C). (C–D) Single-cell pseudotime trajectories of CD4$^+$ and CD8$^+$ T cells estimated using Monocle 3. A continuous value from 0 to 20 was assigned to each cell as a pseudotime. Expression dynamics of skin-residency (E) or T-cell activation (F) markers along the pseudotime of SSc and HC T cells by scatterplots with regression curves.

CCR7, *ITGAE* and *SELL*. This phenotype was further confirmed by the increased expression of *CXCR6* and little to no expression of *KLF2*, *S1PR1* and *SELPLG* (gene for CLA) by these cells (figure 2E and online supplemental figure S3).[20 23–25] In contrast, CD4$^+$ and CD8$^+$ T cells from SSc skin were clearly shifted towards more differentiated states compared with controls and corresponded to several T_{RM} subsets (CD69$^+$ITGAE$^{+/-}$CXCR6$^+$) from earlier to late pseudotime as well as of some recirculating T cells expressing *CCR7*, *SELL*, *KLF2*, *S1PR1* and *SELPLG*, particularly among SSc CD4$^+$ cells at the latest pseudotimes (figure 2E and online supplemental figure S3A). Interestingly, SSc T cells at the latest pseudotimes expressed high levels of activation and effector markers (figure 2F and online supplemental figure S3B) including *HLA-DRA*, *IFNG*, *CRTAM* (CD4$^+$ and CD8$^+$ T cells), *CD40L* and *TNF-A* (CD4$^+$ cells), as well as *GZMB* and *PRF1* (CD8$^+$ T cells). Finally, most SSc CD4$^+$ and CD8$^+$ T cells from early to late pseudotime expressed *CD27* and *CD28*, implying that SSc T cells exhibit an activated effector-memory phenotype.

Single-cell RNAseq identifies a novel CXCL13$^+$ T-cell subset in dcSSc skin lesions

Chemokine *CXCL13* was selectively expressed by most CD4$^+$ T cells from the SSc-specific cluster #7 (figure 3A). Moreover, no other cell type from patient or HC skin samples, apart from a negligible number of SSc CD8$^+$ T cells, expressed *CXCL13* (figure 3A and online supplemental figure S4A,B). These transcriptional results were validated by multicolour immunofluorescence

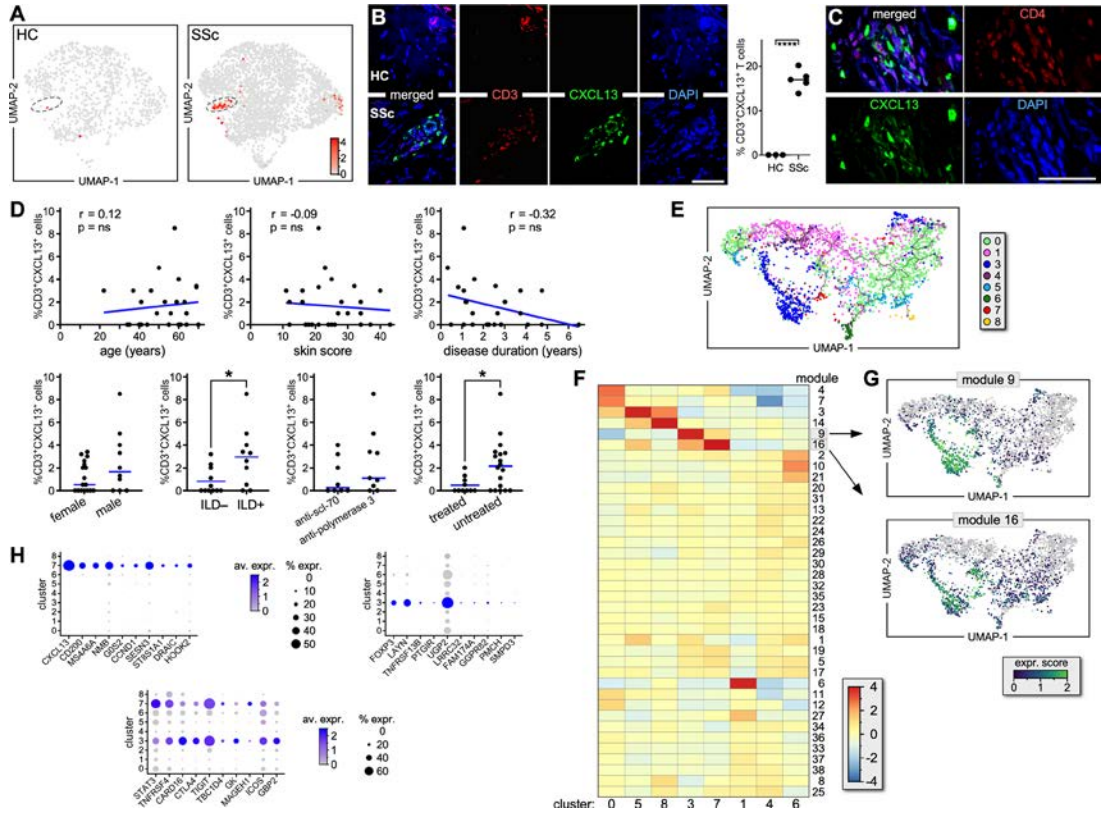


Figure 3 Characterisation of the systemic sclerosis (SSc)-specific CXCL13$^+$ T-cell subset in the lesional skin of patients with active diffuse cutaneous SSc (dcSSc). (A) CXCL13 expression by T lymphocytes from healthy control (HC) (left) and SSc (right) skin samples. (B) Immunofluorescence microscopy shows coexpression of CXCL13 and CD3 in skin samples from active dcSSc (n=5) and HC (n=3). A representative example and the proportion of CD3$^+$CXCL13$^+$ cells are shown. Results are expressed as a percentage of positive cells out of the entire infiltrate following quantification of 8 high-power fields/sample (HPF; magnification ×600). Error bars are mean±SD. Statistics by Student's t-test. (C) Immunofluorescence microscopy shows coexpression of CXCL13 and CD4 in dcSSc skin samples (n=5). A representative experiment is shown at ×1000. (D) Correlation between the frequency of CD3$^+$CXCL13$^+$ cells by scRNAseq and the clinical parameters of patients. (E) Single-cell trajectory of SSc and HC CD4$^+$ T-cell clusters. (F) Heatmap shows gene expression of T-cell clusters based on Louvain-community analysis.[26] (G) Expression transition of genes from modules #16 and 9 along the pseudotime. (H) Dot plots show the proportion of cells and the scaled average gene expression of genes uniquely expressed by CD3$^+$CXCL13$^+$ cells or T regulatory (Tregs) or commonly expressed. ILD, interstitial lung disease; UMAP, Uniform Manifold Approximation and Projection.

microscopy showing several CD3$^+$CXCL13$^+$ cells within perivascular inflammatory infiltrates in the lesional skin of patients with active SSc but not in HC skin samples (figure 3B). Consistently, most CD3$^+$CXCL13$^+$ are CD4$^+$ (figure 3C). Flow cytometry to identify circulating CD4$^+$CXCL13$^+$ T cells in the blood of healthy and dcSSc samples showed no difference in the frequency of this cell type in patients and controls (online supplemental figure S4C–E). Although we detected CD3$^+$CXCL13$^+$ cells in the skin of 44% of the patients tested, we found no statistically significant association between the frequency of CD3$^+$CXCL13$^+$ cells and the skin score of patients or their autoantibody specificity (figure 3D). In contrast, we observed a significant correlation with the presence of interstitial lung disease (ILD) and a trend for increased numbers of CD3$^+$ CXCL13$^+$ cells at the earliest disease stage. The frequency of CD3$^+$CXCL13$^+$ cells did not correlate with the age or sex of patients. Finally, we observed that patients treated with immunosuppressants exhibited a statistically significant lower frequency of CD3$^+$CXCL13$^+$ cells compared with untreated patients (figure 3D).

To understand the CD4$^+$CXCL13$^+$ T cells in the context of SSc CD4$^+$ T-cell differentiation, we constructed a single-cell trajectory for the CD4$^+$ T-cell clusters identified in figure 1C. We observed that CD4$^+$CXCL13$^+$ T cells were located in close proximity to SSc Tregs, suggesting a developmental connection between these two subsets (figure 3E). Contrary to HCs, SSc Tregs upregulated the expression of *ICOS*, *FOXP3*, *IL2RA* and *PPP1CB*, while downregulating the expression of *CTLA4* (online supplemental figure S4F). To reveal gene expression similarities between clusters along the pseudotime, we grouped expressed genes into modules based on Louvain-community analysis (figure 4G).[26] A module heatmap indicates that modules *#6* and 9 exhibit gene expression similarities between Tregs (cluster #3) and CD3$^+$CXCL13$^+$ cells (cluster #7; figure 3F). Indeed, although CD3$^+$CXCL13$^+$ cells and Tregs present distinct transcriptional profiles, they also exhibit common expression of genes not expressed significantly by other T cell populations (figure 3H and online supplemental table S3) such as *STAT3*, *TNFRSF4*, *CTLA4*, *TIGIT*, *ICOS*. Genes uniquely expressed by Tregs include *FOXP3*, *LAYYN*, *TNFRSF13B*, *UGP2*, *PTGIR*, while examples of uniquely expressed gene by CD3$^+$CXCL13$^+$ cells include *CD200*, *MS4A6A*, *DRAIC*, *CCND1*, *G0S2*, *NMB*. Although SSc CD3$^+$CXCL13$^+$ cells express several genes also found in T_{FH} cells,[27] they lack expression of the canonical T_{FH} genes *CXCR5* and *BCL6* (figure 4A and online supplemental figure S4F,G). By immunofluorescence microscopy, we visualised CD3$^+$CXCL13$^+$ cells coexpressing ICOS, TIGIT, CTLA4 as well as producing IL-21 and interferon-γ (IFNγ) (figure 4B–E) in dcSSc skin lesions. Significantly, we also showed that CD3$^+$CXCL13$^+$

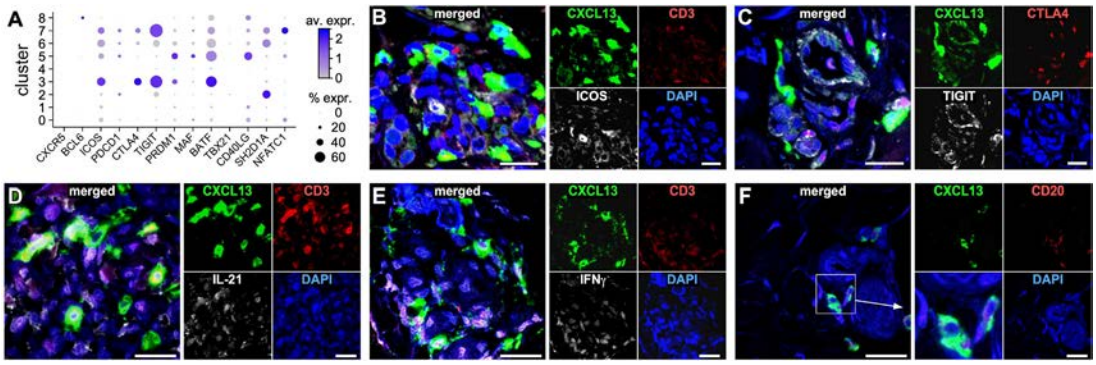


Figure 4 Systemic sclerosis (SSc) CD3$^+$CXCL13$^+$ T cells are a T_{FH}-like subset in inflamed SSc skin. (A) Dot plot showing the proportion of cells and the scaled average gene expression of selected T_{FH} genes[27] by T-cell clusters identified in figure 1C. Multicolour immunofluorescence microscopy visualises coexpression of CXCL13, CD3, ICOS (B), CXCL13, TIGIT, CTLA4 (C), CXCL13, CD3, IL-21 (D), CXCL13, CD3, IFNγ (E), and CXCL13, CD3, CD20 (F) in active diffuse cutaneous SSc (dcSSc) skin samples (n=5). Representative examples are shown at ×1000, inset in (F) is zoomed in three times. DAPI stains nuclei.

cells are adjacent to CD20$^+$ B cells within inflammatory infiltrates of dcSSc skin (figure 4F). Notably, microarray data from multiple early dcSSc patient and control skin samples demonstrated the presence of upregulation of *CXCL13* (online supplemental figure S5, red arrow) in a subset of patients, which was associated with a T-cell and B-cell gene expression signature (eg, *CD3*, *CD247*, *CD8A*, *GZMM*, *GZMH*, *IL15RA*, *CCR7* and *CR2*, *CD19*, *CD22*, *MS4A1,* respectively). Thus, chemokine CXCL13 identifies a T_{FH}-like subset in the lesional skin of dcSSc patients with active skin disease.

DISCUSSION

Abnormal T-cell responses are central in the development of SSc skin disease. Here, we employed scRNAseq to comprehensively profile the transcriptomes of recirculating and resident T cells in the skin lesions of a large cohort of patients with dcSSc. Our analysis provides an unprecedented view of T-cell heterogeneity in SSc skin and identifies a distinct subset that expressed factors enabling B-cell help and likely promoting B-cell responses and possibly autoantibodies production within pathological inflamed skin. Although the role of autoantibodies in SSc is uncertain, they have been implicated in innate immune responses.[28] Furthermore, the perivascular location of T cell infiltration in SSc skin suggests that these cells may play a direct role in vascular damage, the other major driver of SSc clinical disease. Thus, a better understanding of T cell responses in SSc skin disease could lead to more targeted T cell therapy in SSc, an urgent need in view of recent clinical trials, indicating that myeloablation is effective in treating the disease but with significant risks. The specific immune cell targets leading to improved outcomes remain uncertain and targeting T cell activation more generally has not provided a clear clinical benefit.[29] Our observations that only a very specific population of T cells is expanded in SSc skin suggests that these cells are playing a critical role in disease progression and that targeting this selected T cell population might interrupt the disease process.

Recirculating and resident memory T cells play essential roles in localised immune responses in human skin and both populations have been implicated in a variety of inflammatory and autoimmune conditions.[20 23 30–32] Here, we show that while most CD4$^+$ and CD8$^+$ T cells in HC skin are T_{RM}, T cells in SSc lesions are characterised by a combination of skin resident and recirculating T cells (~30%), particularly within the CD4$^+$ T-cell compartment. These cells present a T_{MM}[20] phenotype as they lack *CD69* expression but coexpress *CCR7* and skin homing receptors (*CLA*/*CCR4*). Lack of *SELL* expression by T_{MM} prevents these cells from recirculating via the lymphatics. Rather, SSc T_{MM} cells likely recirculate between blood and skin, in agreement with our previous studies showing skin-tropic T cells in the blood of patients with SSc.[4 5] However, a small fraction of SSc T_{MM} cells coexpress *CCR7* and *SELL* and may recirculate between the blood, skin and non-cutaneous distal lymph nodes. We observed that some T_{MM} cells also coexpress *CD69*, suggesting they may be in a transitional state. While it has been proposed that T_{MM} represent the direct precursors of T_{RM} cells,[20] pathogenic T_{MM} cells might contribute directly to the development of SSc skin disease. As cutaneous T_{RM} cells cannot leave the skin and recirculate nor differentiate into other memory T cell subsets, they are believed to proliferate in situ at a low level.[33] Importantly, we also identified a cluster of proliferating T_{RM} cells (#6) containing a higher number of cells deriving from SSc compared with HC samples. Resident and circulating SSc T cells exhibited a core gene expression signature including various genes involved in adaptive immune responses as well as oxidative phosphorylation and mitochondrial metabolic reprogramming (clusters #4, 6, 7), likely reflecting chronic antigenic stimulation, as described in other autoimmune skin diseases.[34 35] In agreement with our previous studies, demonstrating T-cell plasticity in blood and skin-resident SSc T cells compared with their HC counterparts,[4] we show here that some SSc T_{RM} subsets (clusters #5, 8, 2) upregulate Th1 and Th2 activation pathways and cytokine dysregulation. As previously shown,[36] these T-cell clusters also upregulate the expression of *GATA-3*, the master regulator of type 2 cytokines while maintaining adequate levels of *TBX21*. Interestingly, a recent phase II proof-of-concept study using romilkimab, a novel humanised antibody that neutralises IL-4 and IL-13, in patients with early dcSSc induced a significant reduction in modified Rodnan skin score in patients compared with placebo.[37] Cells from patient samples also differentially express proinflammatory cytokines such *IL-32*, *IL-26*, *IL-16*, which are upregulated in the serum and in the lesional skin of patients with SSc.[38–40] These cytokines have been implicated in the pathogenesis of other inflammatory skin diseases[41–44] by promoting secretion of other inflammatory cytokines (TNFα, IL6) and chemokines (IL8, CXCL2) by macrophages and by acting as chemoattractants and modulators of T-cell activation. Single-cell trajectory analysis indicates that SSc CD4$^+$ and CD8$^+$ T_{RM} cells are distributed throughout pseudotime, while SSc T_{MM} are mostly found in late pseudotime, indicating distinct gene expression. Strikingly, both CD4$^+$ and CD8$^+$ T_{RM} cells from HC

samples were mostly distributed to early pseudotime, whereas SSc T cells were enriched in late pseudotime and were characterised by upregulation of genes associated with an activated effector-memory state. One of the trajectory branches showed enriched expression of primary markers of Tregs (FOXP3, IL2RA) and demonstrate enrichment of ICOS$^+$ Tregs[45] in SSc samples. Several studies indicate that ICOS$^+$ Tregs exhibit strong suppressive potential via upregulation of CTLA-4, GITR (TNFRSF18), LAG3 and TIGIT, as well as IL-10 and TGFβ.[45 46] While we observed that most of these molecules were upregulated in SSc compared with HC Tregs, *CTLA-4*, a major regulator of Treg suppressive function,[47] was downregulated in SSc Tregs, implying a potential functional defect. Additionally, SSc Tregs upregulate the expression of *PPP1CB*, which was shown to make functionally defective Tregs in rheumatoid arthritis (RA) by dephosphorylating FOXP3 at the Ser 418 residue,[48] underlying another potential dysfunction in SSc Tregs.

We identified a subset of CD4$^+$ T cells (cluster #7) in SSc skin that express a core gene signature including *CXCL13*, *CD200*, *MS4A6A*, *ICOS*, *PD1*, *CTLA4*, *TIGIT* and produce high levels of IL21 and IFNγ. A T-cell subset with a similar phenotype (CD4$^+$CXCL13$^+$CXCR5$^-$) was recently described in the synovium and peripheral blood of patients with RA as well as in the tumour microenvironment of breast cancer (BC).[49–51] This subset, named TFHX13 for the high-level expression of the signature chemokine CXCL13, phenotypically resembled T_{FH} cells and was linked with long-term survival and an increase in tumor-infiltrating lymphocytes in BC, whereas was associated with progressive disease in RA.[50 51] Both studies showed that infiltrating TFHX13 cells induce B cell responses by promoting tissue-localised T-cell–B-cell interactions and contribute to the development of tertiary lymphoid structures (TLOs). CXCL13 is a potent B-cell chemoattractant and a key factor for TLO formation.[52] Significantly, we showed by microarray analysis of cutaneous biopsies from patients with early dcSSc upregulation of *CXCL13* in a distinct subset of patients, which was associated with a T-cell and a B-cell gene expression signature. Our data indicate that CD3$^+$CXCL13$^+$ cells colocalise with B cells in inflamed dcSSc skin, suggesting in situ interactions as seen also in RA synovial tissues. Moreover, other studies observed upregulation of CXCL13 in the serum of patients with SSc that correlates with disease severity,[53] as well as in idiopathic pulmonary fibrosis, where CXCL13 represents a prognostic marker.[54] Intriguingly, our data indicate a significant correlation between increased frequencies of skin recirculating CD3$^+$CXCL13$^+$ cells and ILD in the patients tested, warranting further investigation on the role this cell type in ILD pathogenesis. However, the frequency of CD3$^+$CXCL13$^+$ cells did not correlate with the skin score. We have known for several years that bulk SSc skin gene expression of T cell markers does not generally correlate well with the skin score.[55] The perivascular location of the CXCL13 T cells and lymphoid aggregates in the skin suggests that CXCL13 T cells are more important in the vascular disease in SSc than the fibrotic disease manifestations. These findings, as well as our observation that the frequency of CD3$^+$CXCL13$^+$ cells was significantly lower in patients treated with immunosuppressants, suggest that a comprehensive study based on a larger patient cohort with complete clinical details is necessary for understanding the pathogenic mechanisms at the clinical level.

Taylor *et al* recently identified a similar subset of T_{FH}-like cells (CD4$^+$ICOS^{high}PD-1^{high}CXCR5$^+$BCL6$^+$) in SSc skin that contributed to dermal fibrosis via IL-21 production and that correlated with disease scores.[6] Moreover, Ricard *et al*[56] observed that circulating T_{FH} cells (CD4$^+$CXCR5$^+$PD1$^+$BCL6$^+$) correlate with disease severity in SSc and induce B-cell differentiation into plasmablasts secreting immunoglobulin (Ig) via IL-21 production. In comparison, we show that SSc CD3$^+$CXCL13$^+$ cells express lower levels of *ICOS* and *PD1*, lack expression of the canonical T_{FH} markers *BCL6* and *CXCR5*, and express a T_{MM} phenotype, suggesting a potentially distinct migratory capacity within inflamed skin. While BCL6 was long considered critical for IL-21 production, recent studies indicate that MAF may be involved instead[27] and indeed we found upregulation of *MAF* in SSc CD3$^+$CXCL13$^+$ cells. Our data suggest that CD3$^+$CXCL13$^+$ cells are developmentally connected with ICOS$^+$ Tregs. Significantly, studies in SLE show that high ICOS$^+$ Tregs frequencies correlate positively with disease activity scores and serum autoantibody titre,[57] and suggest that ICOS$^+$ Tregs might represent the precursors of inflammatory cells. Thus, SSc CD3$^+$CXCL13$^+$ T cells may represent a distinct T_{FH} subset that differentiates from conversion of ICOS$^+$ Tregs and which is uniquely poised to promote B-cell responses and antibody production within pathologically inflamed non-lymphoid SSc skin lesions.

In conclusion, single-cell transcriptome profiling provides novel insights into SSc pathogenesis by revealing specific landscapes of T lymphocyte subsets. A better understanding of the immunological mechanisms underlying disease processes will lead to novel and targeted therapeutic approaches in SSc, thus realising the goal of precision medicine.

Contributors AMG and TT performed experiments and data analysis; RD, DK and RL acquired samples and collected clinical descriptions; RL contributed to project development and to manuscript preparation; PF developed the project, performed experiments, analysed data and prepared the manuscript.

Funding This work was supported by the National Institutes of Health grant P50-AR060780 (principal investigator: RL) and by the Pittsburgh Autoimmunity Center of Excellence in Rheumatology (PACER) to PF.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Research protocols involving human subjects were approved by the Institutional Review Boards of the Universities of Pittsburgh and Michigan.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All scRNA-seq data have been deposited in the Gene Expression Omnibus: GSE138669.

ORCID iDs
Robyn Domsic http://orcid.org/0000-0002-2765-0922
Dinesh Khanna http://orcid.org/0000-0003-1412-4453
Patrizia Fuschiotti http://orcid.org/0000-0003-1051-5262

REFERENCES

1 Denton CP, Khanna D. Systemic sclerosis. *Lancet* 2017;390:1685–99.
2 Fuschiotti P. T cells and cytokines in systemic sclerosis. *Curr Opin Rheumatol* 2018;30:594–9.
3 Chizzolini C, Boin F. The role of the acquired immune response in systemic sclerosis. *Semin Immunopathol* 2015;37:519–28.
4 Li G, Larregina AT, Domsic RT, *et al*. Skin-Resident Effector Memory CD8$^+$CD28$^-$ T Cells Exhibit a Profibrotic Phenotype in Patients with Systemic Sclerosis. *J Invest Dermatol* 2017;137:1042–50.
5 Fuschiotti P, Larregina AT, Ho J, *et al*. Interleukin-13-producing CD8+ T cells mediate dermal fibrosis in patients with systemic sclerosis. *Arthritis Rheum* 2013. ; ;65:236–46. Jan.

6 Taylor DK, Mittereder N, Kuta E, *et al*. T follicular helper-like cells contribute to skin fibrosis. *Sci Transl Med* 2018;10. doi:10.1126/scitranslmed.aaf5307. [Epub ahead of print: 07 03 2018].
7 Guggino G, Lo Pizzo M, Di Liberto D, *et al*. Interleukin-9 over-expression and T helper 9 polarization in systemic sclerosis patients. *Clin Exp Immunol* 2017;190:208–16.
8 Mathian A, Parizot C, Dorgham K, *et al*. Activated and resting regulatory T cell exhaustion concurs with high levels of interleukin-22 expression in systemic sclerosis lesions. *Ann Rheum Dis* 2012;71:1227–34.
9 MacDonald KG, Dawson NAJ, Huang Q, *et al*. Regulatory T cells produce profibrotic cytokines in the skin of patients with systemic sclerosis. *J Allergy Clin Immunol* 2015;135:946–9.
10 Maehara T, Kaneko N, Perugino CA, *et al*. Cytotoxic CD4+ T lymphocytes may induce endothelial cell apoptosis in systemic sclerosis. *J Clin Invest* 2020;130:2451–64.
11 Fuschiotti P. T cells in SSc skin lesions: knowing your enemy. *Nat Rev Rheumatol* 2020;16:253–4.
12 Macosko EZ, Basu A, Satija R, *et al*. Highly parallel genome-wide expression profiling of individual cells using Nanoliter droplets. *Cell* 2015;161:1202–14.
13 LeRoy EC, Black C, Fleischmajer R, *et al*. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988;15:202–5.
14 Steen VD, Medsger TA. Severe organ involvement in systemic sclerosis with diffuse scleroderma. *Arthritis Rheum* 2000;43:2437–44.
15 Medsger TA, Bombardieri S, Czirjak L, *et al*. Assessment of disease severity and prognosis. *Clin Exp Rheumatol* 2003;21:S42–6.
16 Gaydosik AM, Tabib T, Geskin LJ, *et al*. Single-Cell lymphocyte heterogeneity in advanced cutaneous T-cell lymphoma skin tumors. *Clin Cancer Res* 2019;25:4443–54.
17 Gaydosik AM, Queen DS, Trager MH, *et al*. Genome-Wide transcriptome analysis of the STAT6-regulated genes in advanced-stage cutaneous T-cell lymphoma. *Blood* 2020;136:1748–59.
18 Korsunsky I, Millard N, Fan J, *et al*. Fast, sensitive and accurate integration of single-cell data with harmony. *Nat Methods* 2019;16:1289–96.
19 Krämer A, Green J, Pollard J, *et al*. Causal analysis approaches in ingenuity pathway analysis. *Bioinformatics* 2014. ; ;30:523–30. Feb 15.
20 Watanabe R, Gehad A, Yang C, *et al*. Human skin is protected by four functionally and phenotypically discrete populations of resident and recirculating memory T cells. *Sci Transl Med* 2015;7:279ra239.
21 Cao J, Spielmann M, Qiu X, *et al*. The single-cell transcriptional landscape of mammalian organogenesis. *Nature* 2019;566:496–502.
22 Trapnell C, Cacchiarelli D, Grimsby J, *et al*. The dynamics and regulators of cell fate decisions are revealed by pseudotemporal ordering of single cells. *Nat Biotechnol* 2014;32:381–6.
23 Szabo PA, Levitin HM, Miron M, *et al*. Single-Cell transcriptomics of human T cells reveals tissue and activation signatures in health and disease. *Nat Commun* 2019;10:4706.
24 Milner JJ, Toma C, Yu B, *et al*. Runx3 programs $CD8^+$ T cell residency in non-lymphoid tissues and tumours. *Nature* 2017;552:253–7.
25 Skon CN, Lee J-Y, Anderson KG, *et al*. Transcriptional downregulation of S1pr1 is required for the establishment of resident memory CD8+ T cells. *Nat Immunol* 2013;14:1285–93.
26 Feng C, Liu S, Zhang H, *et al*. Dimension reduction and clustering models for single-cell RNA sequencing data: a comparative study. *Int J Mol Sci* 2020;21. doi:10.3390/ijms21062181. [Epub ahead of print: 22 Mar 2020].
27 Jogdand GM, Mohanty S, Devadas S. Regulators of Tfh cell differentiation. *Front Immunol* 2016;7:520.
28 Kim D, Peck A, Santer D, *et al*. Induction of interferon-alpha by scleroderma sera containing autoantibodies to topoisomerase I: association of higher interferon-alpha activity with lung fibrosis. *Arthritis Rheum* 2008;58:2163–73.
29 Khanna D, Spino C, Johnson S, *et al*. Abatacept in early diffuse cutaneous systemic sclerosis: results of a phase II investigator-initiated, multicenter, double-blind, randomized, placebo-controlled trial. *Arthritis Rheumatol* 2020;72:125–36.
30 Ho AW, Kupper TS. T cells and the skin: from protective immunity to inflammatory skin disorders. *Nat Rev Immunol* 2019;19:490–502.
31 Szabo PA, Miron M, Farber DL. Location, location, location: tissue resident memory T cells in mice and humans. *Sci Immunol* 2019;4. doi:10.1126/sciimmunol.aas9673. [Epub ahead of print: 05 04 2019].
32 Schenkel JM, Masopust D. Tissue-Resident memory T cells. *Immunity* 2014;41:886–97.
33 Park SL, Zaid A, Hor JL, *et al*. Local proliferation maintains a stable pool of tissue-resident memory T cells after antiviral recall responses. *Nat Immunol* 2018;19:183–91.
34 Geltink RIK, Kyle RL, Pearce EL. Unraveling the complex interplay between T cell metabolism and function. *Annu Rev Immunol* 2018;36:461–88.
35 Yang Z, Fujii H, Mohan SV, *et al*. Phosphofructokinase deficiency impairs ATP generation, autophagy, and redox balance in rheumatoid arthritis T cells. *J Exp Med* 2013;210:2119–34.
36 Cascio S, Medsger TA, Hawse WF, *et al*. 14-3-3z sequesters cytosoli$_c$ T-bet, upregulating IL-13 levels in T_c2 and $CD8^+$ lymphocytes from patients with scleroderma. *J Allergy Clin Immunol* 2018;142:e106:109–19.
37 Allanore Y, Wung P, Soubrane C, *et al*. A randomised, double-blind, placebo-controlled, 24-week, phase II, proof-of-concept study of romilkimab (SAR156597) in early diffuse cutaneous systemic sclerosis. *Ann Rheum Dis* 2020;79:1600–7.
38 Di Benedetto P, Guggino G, Manzi G, *et al*. Interleukin-32 in systemic sclerosis, a potential new biomarker for pulmonary arterial hypertension. *Arthritis Res Ther* 2020;22:127.
39 Zhou Y, Hou W, Xu K, *et al*. The elevated expression of Th17-related cytokines and receptors is associated with skin lesion severity in early systemic sclerosis. *Hum Immunol* 2015;76:22–9.
40 Kawabata K, Makino T, Makino K, *et al*. IL-16 expression is increased in the skin and sera of patients with systemic sclerosis. *Rheumatology* 2020;59:519–23.
41 Itoh T, Hatano R, Komiya E, *et al*. Biological effects of IL-26 on T cell-mediated skin inflammation, including psoriasis. *J Invest Dermatol* 2019;139:878–89.
42 Kamijo H, Miyagaki T, Hayashi Y, *et al*. Increased IL-26 Expression Promotes T Helper Type 17- and T Helper Type 2-Associated Cytokine Production by Keratinocytes in Atopic Dermatitis. *J Invest Dermatol* 2020;140:e632:636–44.
43 Meyer N, Zimmermann M, Bürgler S, *et al*. IL-32 is expressed by human primary keratinocytes and modulates keratinocyte apoptosis in atopic dermatitis. *J Allergy Clin Immunol* 2010;125:e810:858–65.
44 Kempuraj D, Conti P, Vasiadi M, *et al*. Il-32 is increased along with tryptase in lesional psoriatic skin and is up-regulated by substance P in human mast cells. *Eur J Dermatol* 2010;20:865–7.
45 Li D-Y, Xiong X-Z. $ICOS^+$ Tregs: A Functional Subset of Tregs in Immune Diseases. *Front Immunol* 2020;11:2104.
46 Miragaia RJ, Gomes T, Chomka A, *et al*. Single-Cell transcriptomics of regulatory T cells reveals trajectories of tissue adaptation. *Immunity* 2019;50:e497:493–504.
47 Rudd CE. CTLA-4 co-receptor impacts on the function of Treg and CD8+ T-cell subsets. *Eur J Immunol* 2009;39:687–90.
48 Nie H, Zheng Y, Li R, *et al*. Phosphorylation of FOXP3 controls regulatory T cell function and is inhibited by TNF-α in rheumatoid arthritis. *Nat Med* 2013;19:322–8.
49 Gu-Trantien C, Willard-Gallo K. PD-1(hi)CXCR5(-)CD4(+) TFH Cells Play Defense in Cancer and Offense in Arthritis. *Trends Immunol* 2017;38:875–8.
50 Gu-Trantien C, Migliori E, Buisseret L, *et al*. CXCL13-producing TFH cells link immune suppression and adaptive memory in human breast cancer. *JCI Insight* 2017;2. doi:10.1172/jci.insight.91487. [Epub ahead of print: 02 Jun 2017].
51 Rao DA, Gurish MF, Marshall JL, *et al*. Pathologically expanded peripheral T helper cell subset drives B cells in rheumatoid arthritis. *Nature* 2017;542:110–4.
52 Ansel KM, Ngo VN, Hyman PL, *et al*. A chemokine-driven positive feedback loop organizes lymphoid follicles. *Nature* 2000;406:309–14.
53 Wutte N, Kovacs G, Berghold A, *et al*. 13 and B-cell activating factor as putative biomarkers in systemic sclerosis. *Br J Dermatol* 2013;169:723–5.
54 Vuga LJ, Tedrow JR, Pandit KV, *et al*. C-X-C motif chemokine 13 (CXCL13) is a prognostic biomarker of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2014;189:966–74.
55 Milano A, Pendergrass SA, Sargent JL, *et al*. Molecular subsets in the gene expression signatures of scleroderma skin. *PLoS One* 2008;3:e2696.
56 Ricard L, Jachiet V, Malard F, *et al*. Circulating follicular helper T cells are increased in systemic sclerosis and promote plasmablast differentiation through the IL-21 pathway which can be inhibited by ruxolitinib. *Ann Rheum Dis* 2019;78:539–50.
57 Liu Y, Zhu T, Cai G, *et al*. Elevated circulating CD4+ ICOS+ Foxp3+ T cells contribute to overproduction of IL-10 and are correlated with disease severity in patients with systemic lupus erythematosus. *Lupus* 2011;20:620–7.
58 Satija R, Farrell JA, Gennert D, *et al*. Spatial reconstruction of single-cell gene expression data. *Nat Biotechnol* 2015;33:495–502.

EPIDEMIOLOGICAL SCIENCE

Familial aggregation and heritability: a nationwide family-based study of idiopathic inflammatory myopathies

Weng Ian Che ,[1] Helga Westerlind ,[1] Ingrid E Lundberg ,[2,3] Karin Hellgren ,[1,2,3] Ralf Kuja-Halkola ,[4] Marie Holmqvist [1,2,3]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-219914).

[1]Clinical Epidemiology Division, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden
[2]Division of Rheumatology, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden
[3]Rheumatology, Gastro. Derm, Rheuma, Karolinska Institutet Hospital, Stockholm, Sweden
[4]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Correspondence to
Weng Ian Che, Clinical epidemiology division, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Stockholm, Sweden; weng.ian.che@ki.se

Received 14 January 2021
Accepted 31 May 2021
Published Online First 15 June 2021

To cite: Che WI, Westerlind H, Lundberg IE, *et al*. *Ann Rheum Dis* 2021;**80**:1461–1466.

ABSTRACT

Objectives The magnitude of the genetic contribution to idiopathic inflammatory myopathies (IIMs) is unknown. In this project, we aimed to investigate the familial aggregation and heritability of IIM.

Methods This is a family-based study using nationwide healthcare register data in Sweden. We matched each patient with IIM to individuals without IIM, identified their first-degree relatives and determined the IIM status among all first-degree relatives. We estimated the adjusted ORs (aORs) of familial aggregation of IIM using conditional logistic regression. In addition, we used tetrachoric correlation to estimate the heritability of IIM.

Results We included 7615 first-degree relatives of 1620 patients with IIM diagnosed between 1997 and 2016 and 37 309 first-degree relatives of 7797 individuals without IIM. Compared with individuals without IIM, patients with IIM were more likely to have ≥1 first-degree relative affected by IIM (aOR=4.32, 95% CI 2.00 to 9.34). Furthermore, the aOR of familial aggregation of IIM in full siblings was 2.53 (95% CI 1.62 to 3.96). The heritability of IIM was 22% (95% CI 12% to 31%) among any first-degree relatives and 24% (95% CI 12% to 37%) among full siblings.

Conclusions IIM has a familial component with a risk of aggregation among first-degree relatives and a heritability of about 20%. This information is of importance for future aetiological studies and in clinical counselling.

Key messages

What is already known about this subject?

► Previous family-based studies and genome-wide association studies of idiopathic inflammatory myopathies (IIMs) suggest a genetic predisposition to IIM. However, how much genetics contribute to IIM remains unclear.

What does this study add?

► Family history of IIM in first-degree relatives is associated with the occurrence of IIM.
► Additive genetic factors explain 22% of the variation of IIM in the Swedish population within the study period. Compared with the SNP-based heritability of IIM, our heritability estimate of IIM is much higher, implying that there are unknown genetic variants associated with IIM to be discovered.

How might this impact on clinical practice or future developments?

► Our findings provide new insight into the genetic predisposition to IIM and implicate the potential of using family history of IIM as an indicator in the diagnostic workup.

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are rare systemic inflammatory diseases of partly unknown pathogenesis.[1] Onset and progression of IIM is influenced both by environmental and genetic factors, but the exact interplay between these factors remains unclear.[1 2] Recently, genome-wide association studies (GWASs) confirmed that alleles in the human leucocyte antigen (HLA) 8.1 ancestral haplotype—HLA-DRB1*03:01 and HLA-B*08:01—are important genetic risk factors for IIM.[3–6] Other genes outside the HLA region such as PTPN22 have also been suggested. Although there are established genetic risk factors for IIM, the impact of genetics on the risk of developing IIM is unknown.

Investigating the degree to which a disease aggregates in families (familial aggregation) and how much of the phenotypic variance of a disease is explained by the genetic variance in a population (heritability) may provide insight on the genetic contribution to that disease.[7 8] Evidence in the literature indicating familial aggregation of IIM is conflicting. There are several case reports and one population-based family study supporting familial aggregation,[9–16] while other family-based studies failed to detect any.[17–19]

Previously published heritability estimates in IIM are based on GWAS data, where about 8.3% of the phenotypic variance for polymyositis (PM) and 5.5% of the variance for dermatomyositis (DM) is explained by the genetic variance in the studied population.[20] These estimates are unlikely to reflect the true heritability of IIM, partly since they are based on data from GWAS where only single nucleotide polymorphisms (SNPs) of selected loci are genotyped, but they can serve as a lower bound.[21 22] Heritability can also be estimated using family data.[8] Estimates from this method are generally considered as the upper bound of heritability since they may include the influence of other similarities, besides genetics, among relatives. As far as

we know, there are no studies reporting the heritability of IIM using family-based designs.

Knowing more about the genetic predisposition to IIM could improve our understanding of the underlying aetiology of the disease. We therefore set out to investigate the familial aggregation and heritability of IIM using nationwide register data in Sweden.

METHODS

Study setting and data sources

The healthcare system in Sweden is primarily tax funded, which ensures equal access for all residents. The *National Patient Register* (*NPR*) was established in 1964 and prospectively collects data on inpatient care with virtually 100% coverage since 1987. Since 2001, it includes around 80% of all non-primary outpatient visits, and missing visits are primarily from private practice.[23] Patients with IIM are exclusively managed by hospital-based rheumatologists.

The *Multi-Generation Register* (*MGR*) includes information on parents, siblings and children of all individuals born later than 1931 and registered in Sweden since 1 January 1961. The ascertainment of parents of individuals born in Sweden in 1952 and afterwards is above 90%.[24]

The *Total Population Register* (*TPR*), founded in 1968, has data on nearly 100% of births and deaths in Sweden and is often used to randomly sample comparators from the general population in research.[25]

Study population

We included all patients having ≥1 hospitalisation with IIM as main diagnosis between 1997 and 2000 in the NPR. Between 2001 and 2016, when both inpatient and outpatient data were available, we included all patients having ≥2 outpatient visits or hospitalisations with IIM whereof at least one had IIM as the main diagnosis. We only considered International Classification of Diseases (ICD), 10 codes M33 and G72.4 from internal medicine, rheumatology, dermatology, neurology or paediatrics department. Patients are only assigned these ICD codes when the medical assessments are completed, and the diagnosis of IIM is certain. This includes excluding potential IIM-mimics.[26] The algorithm used to identify IIM has been found to be robust, and the ICD codes have been validated with a positive predictive value up to 96% using clinician-entered diagnosis from the Swedish Rheumatology Quality Register as gold standard.[27 28] We further categorised IIM into DM (M33.1), other IIM (M33.2, M33.9 and G72.4) and juvenile IIM (JIIM) (M33 or G72.4 with age ≤18 years at diagnosis). We randomly matched each patient with IIM with up to five individuals without IIM from the TPR. The matching factors were sex, birth year and residential area at the time of IIM diagnosis in their matched patient with IIM. All individuals without IIM were alive and living in Sweden at match date. We only included patients with IIM and individuals without IIM (collectively referred to as index individuals) who were born in Sweden in 1932 and onwards to increase ascertainment of their biological first-degree relatives. The study population mainly includes individuals of Caucasian ethnicity. Via linkage to the MGR and the TPR, we ascertained their parents, full siblings and offspring, as well as data on sex and birth year of first-degree relatives. As exposure status to IIM could not be determined before 1987, we only included first-degree relatives who were alive in 1987. Lastly, we excluded index individuals without any first-degree relatives identified.

Identification of IIMs in first-degree relatives

In the primary analyses, we required first-degree relatives to have ≥1 visit with IIM as main diagnosis in the NPR between 1987 and 2017 to be considered as exposed. The ICD 9 codes used for the period between 1987 and 1996 were 710D and 710E. We also performed a sensitivity analysis where we used a stricter definition, the same definition of IIM as we used for index individuals, to determine IIM in first-degree relatives.

Identification of muscular dystrophies and metabolic myopathies

To examine the risk of misdiagnosing inherited myopathies as IIM, we went through all the main diagnoses of inpatient and outpatient visits registered between 1987 and 2017 of individuals in the family units affected by IIM to identify diagnoses of muscular dystrophies and metabolic myopathies (online supplemental table 1).

Statistical methods

We described the demographic characteristics and the family structure between patients with IIM and individuals without IIM. Variables were described using mean (SD) and median (first and third quartiles) or frequencies with proportions.

Familial aggregation of IIMs

In this family-based design, we treated IIM in index individuals as the outcome and IIM in first-degree relatives as the exposure. We used logistic regression conditioning on the matching cluster to estimate the adjusted ORs (aORs) of having first-degree relatives affected by IIM in patients with IIM compared with individuals without IIM. We performed the analyses by number of affected relatives and by treating each first-degree kinship pair as an independent unit and using a robust sandwich variance estimator to control SEs for familial clustering. We additionally adjusted for sex and birth year of first-degree relatives in the second modelling method.

Heritability of IIMs

Given the population data used in this study, we estimated the heritability of IIM overall and among full siblings using the tetrachoric correlation based on several assumptions: (1) a normally distributed liability model of IIM with a disease threshold; (2) no assortative mating; (3) that the genetic variance was solely due to additive genetic effects; and (4) that the only similarity between first-degree relatives was genetics. For example, no environmental factors shared between siblings were assumed to contribute to disease liability.[7 29] Thus, the provided heritability estimate is a narrow sense heritability where only additive genetic effects, the sum of average effects of disease-associated alleles, are considered.[7] We created a 2×2 contingency table presenting the concordant and discordant relative pairs of patients with IIM and individuals without IIM. Since the ascertainment of individuals without IIM was a subsample of the entire population, we adjusted the calculation by the observed prevalence of IIM in Sweden (0.014%)[27] and used the observed OR of IIM associated with having first-degree relatives affected by IIM for calculation. These calculations have been described in detail elsewhere.[30] The intraclass correlation coefficient divided by the degree of relatedness, 0.5 for first-degree relatives, was considered the heritability of IIM.[7] We repeated the analyses by varying the prevalence between 0.004% and 0.024% to test the robustness of heritability to changes of IIM prevalence in the population.

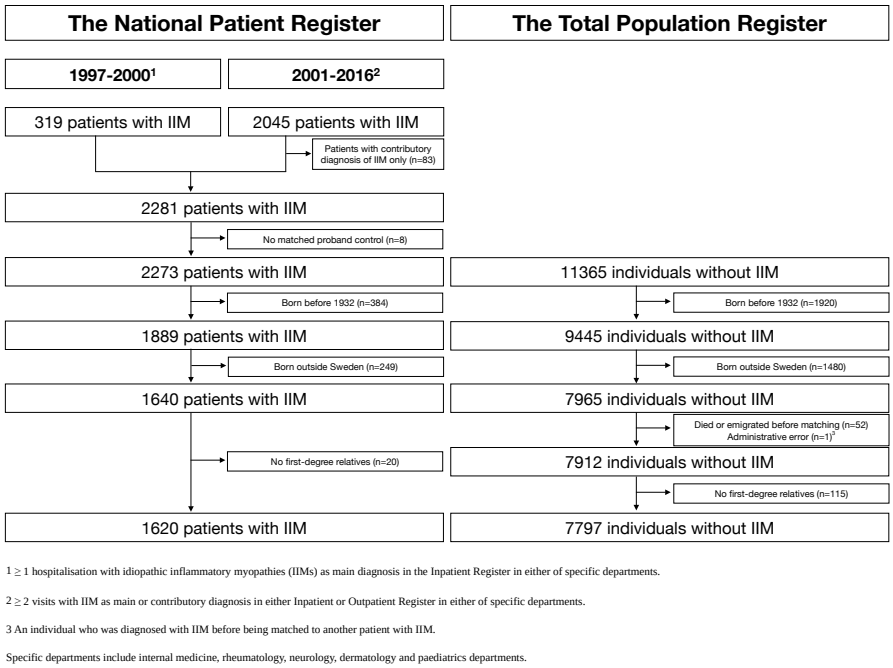


Figure 1 Identification of patients with idiopathic inflammatory myopathies (IIMs) and individuals without IIM from the National Patient Register and the Total Population Register, respectively.

Sensitivity analyses

We repeated all analyses using the above-mentioned stricter definitions to define IIM in first-degree relatives. This was done to test the robustness of the main analyses. As the outpatient register was not nationwide until 2001, we repeated the analyses by including only first-degree relatives who were alive in 2001.

We primarily used SAS V.9.4 (SAS Institutet) for data management and analyses, except for tetrachoric correlations, which were estimated in R V.3.6.1[31] using the R-package *polycor*.[32] As this was an entirely register-based study, we did not collect patient consent.

Patient and public involvement

We did not involve patients in any stage of this study.

RESULTS

This study included 1620 patients with IIM and 7797 individuals without IIM (figure 1 and online supplemental table 2). Of 1620 patients with IIM, 951 (59%) were women, and the median birth year was 1949. The median age at inclusion was 57 years. Eight per cent of the patients were diagnosed with JIIM, 31% with DM and 61% with other IIM (table 1). The number of patients with prevalent IIM ascertained by calendar year since 2001 were generally stable (online supplemental figure 1). Other characteristics and family structure were similar between the patients with IIM and individuals without IIM (table 2). The mean (SD) number of first-degree relative per family unit was 4.7 (2.2) in patients with IIM and 4.8 (2.1) in individuals without IIM.

Familial aggregation of IIMs

Thirteen (0.8%, 9 family units) of 1620 patients with IIM had at least one first-degree relative affected by IIM versus 16 (0.2%, 16 family units) in 7797 individuals without IIM, corresponding to an aOR of 4.32 (95% CI 2.00 to 9.34) (table 3). All cases of familial IIM were 45 years of age or above when diagnosed, and none of the individuals had any visits indicating a main diagnosis of muscular dystrophies or metabolic myopathies. Seven of the nine family units affected by IIM had concordant diagnoses of other IIM. The aOR of familial aggregation decreased to 2.61 but remained significant with a narrower 95% CI (1.80 to 3.79) when all first-degree kinship pairs were treated as independent units. Proportions of IIM were higher in all types of first-degree kinship in patients with IIM compared with individuals without IIM. We only estimated the aOR (2.53, 95% CI 1.62 to 3.96) for full siblings since the number of cases of IIM in individuals with affected parents or offspring in both groups were <5.

Table 1 Characteristics of patients with idiopathic inflammatory myopathies (IIMs) and individuals without IIM*

	Patients with IIM (n=1620)	Individuals without IIM (n=7797)
Women, n (%)	951 (59)	4639 (60)
Birth year, median (Q1–Q3)	1949 (1941–1964)	1949 (1941–1964)
Living in Southern Sweden, n (%)	1342 (83)	6455 (83)
Age at inclusion, median (Q1–Q3)	57 (44–66)	57 (44–65)
IIM subtypes, n (%)		
Juvenile IIM†	128 (8)	–
Dermatomyositis‡	501 (31)	–
Other IIM§	991 (61)	–

*Q1: the first quartile; Q3: the third quartile.
†Age at diagnosis ≤18 years of age.
‡With diagnostic code M33.1 and age at diagnosis >18 years of age.
§With diagnostic code M33.2, M33.9 or G72.4 and age at diagnosis >18 years of age.

Table 2 Family structures of patients with idiopathic inflammatory myopathies (IIMs) and individuals without IIM, and demographic characteristics of their first-degree relatives*

	Patients with IIM		Individuals without IIM	
Any first-degree relatives, n, mean±SD	7615	4.7±2.2	37 309	4.8±2.1
Parents	2306	1.4±0.8	11 414	1.5±0.7
Women, n (%)	1253 (54)		6314 (55)	
Birth year, median (Q1–Q3)	1926 (1916–1943)		1926 (1916–1943)	
Full siblings	2464	1.5±1.5	11 685	1.5±1.5
Women, n (%)	1238 (50)		5863 (50)	
Birth year, median (Q1–Q3)	1951 (1943–1962)		1950 (1943–1963)	
Offspring	2845	1.8±1.3	14 210	1.8±1.3
Women, n (%)	1335 (47)		6960 (49)	
Birth year, median (Q1–Q3)	1975 (1966–1987)		1975 (1967–1989)	

*Q1: the first quartile; Q3: the third quartile.

Heritability of IIMs

The overall heritability of IIM among any first-degree relative was 22% (95% CI 12% to 31%) when the underlying prevalence of IIM was assumed to be 0.014% and the observed OR in the 2×2 table was 3.99. With the same assumed prevalence of IIM, the point estimate of the heritability of IIM among full siblings increased slightly to 24% (95% CI 12% to 37%) with an observed OR of 4.28 in the contingency table. Varying the assumed prevalence of IIM in the population between 0.004% and 0.024% did not affect the result (figure 2).

Sensitivity analyses

Results of analyses using a stricter definition to define IIM among first-degree relatives or analyses including only relatives alive in 2001 were in line with the findings of the primary analyses (online supplemental tables 3–6).

DISCUSSION

This is the first population-based family study that estimates the genetic contribution to IIM based on familial aggregation and heritability. We found that having at least one first-degree relative affected by IIM was strongly associated with the risk of developing IIM, and above one-fifth of the phenotypic variance of IIM could be attributed to additive genetic variance in the Swedish population.

Prior to our study, several studies have attempted to examine the familial aggregation of IIM with family-based[17 18] and population-based methods.[19] None of the studies found any significant associations, probably due to insufficient statistical power. The study of Ginn *et al*[17] including 151 first-degree relatives of 21 patients with IIM reported only one familial DM. Similarly, there were only three cases of familial DM in a study including first-degree to third-degree relatives of 304 children with juvenile DM, resulting in a non-significant OR=3.00 with wide 95% CI (0.31 to 28.9).[18] A Danish nationwide register study including 949 patients with dermato-polymyositis presented a familial OR of 3.9 (95% CI 0.6 to 27.7) for parents or siblings.[19] In our study, which increased the number of patients with IIM by 70%, we found a similar but statistically significant point estimate of familial aggregation of IIM, suggesting that the non-significances in previous studies might be mainly due to insufficient statistical power. Recently, a study by Thomsen *et al*[16] comprising 2668 patients with an ICD code suggesting IIM between 1964 and 2012 also observed familial aggregation of IIM for parents and siblings (standardised incidence ratio=4.03, 95% CI 1.27 to 8.35), a finding that is in line with our results.

Our heritability estimate of 22% was higher than previously published SNP-based heritability (5.5% for DM and 8.3% for PM).[20] This is to be expected for several reasons. First, in SNP-based heritability, the SNPs with mild or moderate effects on a trait that do not reach statistical significance are not included in the calculations,[21] something that could lead to an underestimation of the heritability even though the genome-wide complex trait analysis (GCTA) was used to compensate for this problem.[33 34] Second, the SNP-based heritability in IIM was estimated based on SNPs presented on the Immunochip, where SNPs are selected based on GWAS findings of 12 autoimmune diseases excluding IIM. The Immunochip therefore is not specific to IIM.[22] That is, the SNP-based heritability of IIM already published is likely to only represent a portion of the actual heritability of IIM. In addition, Golan *et al*[35] have previously demonstrated that the GCTA method could underestimate the heritability when a disease is rare.

Table 3 Adjusted ORs (aORs) of having first-degree relatives affected by idiopathic inflammatory myopathies (IIMs) in patients with IIM compared with individual without IIM*

	Patients with IIM, n/N (%)	Individuals without IIM, n/N (%)	aOR† (95% CI)	aOR‡ (95% CI)
≥1 relative	13/1620 (0.80)	16/7797 (0.21)	4.32 (2.00 to 9.34)	–
Any first-degree relatives	13/7615 (0.17)	16/37309 (0.04)	2.61 (1.80 to 3.78)	2.61 (1.80 to 3.79)
Parents	2/2306 (0.09)	5/11414 (0.04)	–	–
Full siblings	9/2464 (0.37)	10/11685 (0.09)	2.54 (1.62 to 3.99)	2.53 (1.62 to 3.96)
Offspring	2/2845 (0.07)	1/14210 (0.01)	–	–

*≥1 relative: comparison between patients with IIM and individuals without IIM; any first-degree relatives, parents, full siblings and offspring: comparison between relative pairs of patients with IIM and relative pairs of individuals without IIM.
†Controlled for sex, birth year and residential area of index persons.
‡Controlled for sex, birth year and residential area of index persons, sex and birth year of first-degree relatives.

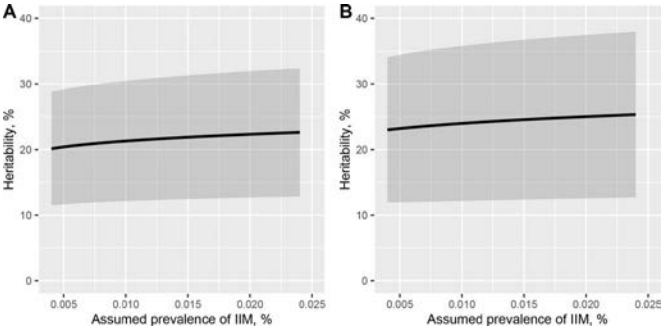


Figure 2 Point estimates with 95% CIs (grey shading) of heritability of IIM using assumed prevalence of IIM ranging from 0.004% to 0.024%, with a fixed interval of 0.0002% for (A) any first-degree relatives and (B) full siblings only. IIM, idiopathic inflammatory myopathy.

In our present study, we estimated heritability by using correlations among first-degree relatives. When doing so, we made several assumptions including that genetics are the only similarity among first-degree relatives. This assumption is unlikely to be true, and if there are environmental factors contributing to disease within a family, we might overestimate the heritability of IIM. However, the results in our study show that the heritability of IIM in all first-degree relatives among those who in general share less environment growing up (ie, parents and offspring are usually exposed to different childhood environments) was similar to that in full siblings who often do share environment growing up. This supports that our findings are not results where shared environmental factors largely explain the variance of IIM.

Estimates of heritability should be interpreted with caution. The heritability estimated in our study tells us the extent of *variation* of IIM explained by additive genetic *variation* and not of how much genes influence the risk of IIM.[7] We should therefore not infer that the probability of IIM being passed from parent to offspring is 22%, a concept that can be expressed as inheritability, or that genetics is less important than non-genetic factors in the development of IIM. Though heritability estimates tell little or even nothing about causal effect of genes on a disease, it is still an important starting point to explore the genetic contribution to a disease where today there are no available methods to estimate inheritability of a complex trait.[36]

Our study suggests that IIM generally has a lower risk of familial aggregation and heritability than some other autoimmune diseases. This may suggest that the pathogenesis of IIM is more complex than the pathogenesis of other autoimmune diseases. For example, the overall familial risk of any first-degree relatives and heritability for rheumatoid arthritis in the Swedish population is 3.2 (95% CI 3.0 to 3.3) and 40%, respectively.[30] For organ-specific autoimmune diseases, even higher estimates have been presented; in a Swedish twin study, the familial risk of coeliac disease was 124 (95% CI 81 to 129) in monozygotic twins.[37] Given that we found a higher heritability of IIM compared with the previously reported SNP-based heritability, there may still be unknown genes contributing to the pathogenesis of IIM. One direction for future research would be to do whole genome sequencing of patients with IIM to discover novel genetic variants associated with IIM, and hence further improve our understanding of the aetiology of IIM.

Our study has several limitations. Due to lack of serological data, we could not examine the familial aggregation and heritability stratified by antibody profiles, nor could we perform analyses stratified by clinical subtypes, age at onset and sex since there were insufficient cases of familial IIM. We could not control for dependence between observations in the tetrachoric correlations, which could mean that our heritability CIs might be too narrow. This would however not affect the point estimate. Also, the generalisability of our findings to other populations should be taken with caution. Genetic variants of IIM vary somewhat across ethnicities.[38] For example, HLA-DRB1*12:02, associated with IIM in a Korean population, is rarely found in Caucasian populations.[39] The heritability estimate is specific to population, time and environment.[36]

Lastly, we could not completely eliminate the risk of misdiagnosing inherited myopathies as IIM. However, we found no diagnoses of muscular dystrophies or metabolic myopathies in the years before and after the IIM diagnosis in individuals with familial IIM in our study. In Sweden, each patient undergoes a muscle biopsy before a diagnosis of IIM is set, and the clinical awareness of IIM mimics among rheumatologists, neurologists and neuropathologists is high.[26] Thus, even if misclassification of IIM mimics as IIM could not entirely be ruled out, we think the risk is low in our clinical setting.

Despite these limitations, our study provides novel insight of the genetic contribution to IIM with validated data and robust analyses. Using high-quality nationwide register data, we have a representative sample of IIM, and our study is well powered. As our data were prospectively collected in the registers, we avoid weaknesses usually associated with case–control studies, such as recall bias. The matched design resulted in even family structures and distributions of sex and birth year of first-degree relatives between patients with IIM and individuals without IIM, minimising bias due to these factors on the estimates.

Our findings do not only improve our understanding of the genetic contribution to IIM but it may also have important clinical implications. In current diagnostic workup of IIM, information on family history of muscle weakness and autoimmunity is useful.[1 26] With our results, we add knowledge on how to assess family history in IIM in the diagnostic workup of IIM.

In conclusion, this study suggests that family history of IIM could influence the risk of IIM and that there are additional genetic risk markers to be identified. This information is important for both our aetiological understanding of IIM and clinical counselling.

Twitter Marie Holmqvist @marie_holmqvist

Contributors All authors conceived and designed the work. WIC and HW contributed to the analysis of data. WIC, HW and MH interpreted and drafted the manuscript, and all authors contributed to revising the manuscript critically and for intellectual content. MH acquired the data had full access to all the data in this study and takes responsibility for the decision to publish. All authors read and approved the final version of manuscript for submission.

Funding MH was supported by the Wallenberg Foundation (Marianne and Marcus Wallenberg Clinical Fellow). The project was supported by the Swedish Rheumatism Association, the King Gustaf V:s 80 years Foundation, the Professor Nanna Svartz Foundation, Region Stockholm (ALF-project) and the Swedish Research Council.

Competing interests IEL has received grants from Swedish Research Council and from Region Stockholm (ALF-project), during the conduct of the study, grants and consulting fee from Bristol Myers Squibb, consulting fee from Corbus Pharmaceutical, grants from Astra Zeneca, research collaboration with aTyr Pharma, outside the submitted work.

Patient consent for publication Not required.

Ethics approval This study was approved by the Swedish Ethical Review Authority. The number of ethical permit was 2017/2000-31.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iDs
Weng Ian Che http://orcid.org/0000-0002-8355-2024
Helga Westerlind http://orcid.org/0000-0003-3380-5342
Ingrid E Lundberg http://orcid.org/0000-0002-6068-9212
Karin Hellgren http://orcid.org/0000-0001-7149-0973
Ralf Kuja-Halkola http://orcid.org/0000-0002-3765-2067
Marie Holmqvist http://orcid.org/0000-0001-8996-5260

REFERENCES

1 Aggarwal R, Oddis CV. *Managing myositis: a practical guide*. Springer International Publishing, 2019.
2 Miller FW, Lamb JA, Schmidt J, *et al*. Risk factors and disease mechanisms in myositis. *Nat Rev Rheumatol* 2018;14:255–68.
3 Miller FW, Chen W, O'Hanlon TP, *et al*. Genome-wide association study identifies HLA 8.1 ancestral haplotype alleles as major genetic risk factors for myositis phenotypes. *Genes Immun* 2015;16:470–80.
4 Rothwell S, Cooper RG, Lundberg IE, *et al*. Dense genotyping of immune-related loci in idiopathic inflammatory myopathies confirms HLA alleles as the strongest genetic risk factor and suggests different genetic background for major clinical subgroups. *Ann Rheum Dis* 2016;75:1558–66.
5 Acosta-Herrera M, Kerick M, González-Serna D, *et al*. Genome-wide meta-analysis reveals shared new *loci* in systemic seropositive rheumatic diseases. *Ann Rheum Dis* 2019;78:311–9.
6 Rothwell S, Chinoy H, Lamb JA, *et al*. Focused HLA analysis in Caucasians with myositis identifies significant associations with autoantibody subgroups. *Ann Rheum Dis* 2019;78:996–1002.
7 Tenesa A, Haley CS. The heritability of human disease: estimation, uses and abuses. *Nat Rev Genet* 2013;14:139–49.
8 Mayhew AJ, Meyre D. Assessing the heritability of complex traits in humans: methodological challenges and opportunities. *Curr Genomics* 2017;18:332–40.
9 Wedgwood RJ, Cook CD, Cohen J. Dermatomyositis; report of 26 cases in children with a discussion of endocrine therapy in 13. *Pediatrics* 1953;12:447–66.
10 Rider LG, Gurley RC, Pandey JP, *et al*. Clinical, serologic, and immunogenetic features of familial idiopathic inflammatory myopathy. *Arthritis Rheum* 1998;41:710–9.
11 Shamim EA, Miller FW. Familial autoimmunity and the idiopathic inflammatory myopathies. *Curr Rheumatol Rep* 2000;2:201–11.
12 Mastaglia F, Price P, Walters S, *et al*. Familial inclusion body myositis in a mother and son with different ancestral MHC haplotypes. *Neuromuscul Disord* 2006;16:754–8.
13 Limaye V, Walker J, Ahern M, *et al*. Monozygotic twins with distinct forms of idiopathic inflammatory myositis. *Rheumatology* 2009;48:855–7.
14 Ozaki T, Yamashita H, Hosono Y, *et al*. Two patients in the same family with anti-ARS antibody-associated myositis. *Mod Rheumatol* 2014;24:699–700.
15 Khosa S, Vazirian S, Mishra S. Familial inclusion body myositis with negative Anti-cytosolic 5′-nucleotidase 1A (cN1A) antibody test. (P3.4-016). *Neurology*2019;92:P3.4–16.
16 Thomsen H, Li X, Sundquist K, *et al*. Familial associations for rheumatoid autoimmune diseases. *Rheumatol Adv Pract* 2020;4:rkaa048.
17 Ginn LR, Lin JP, Plotz PH, *et al*. Familial autoimmunity in pedigrees of idiopathic inflammatory myopathy patients suggests common genetic risk factors for many autoimmune diseases. *Arthritis Rheum* 1998;41:400–5.
18 Niewold TB, Wu SC, Smith M, *et al*. Familial aggregation of autoimmune disease in juvenile dermatomyositis. *Pediatrics* 2011;127:e1239–46.
19 Eaton WW, Rose NR, Kalaydjian A, *et al*. Epidemiology of autoimmune diseases in Denmark. *J Autoimmun* 2007;29:1–9.
20 Rothwell S, Lamb JA, Chinoy H. New developments in genetics of myositis. *Curr Opin Rheumatol* 2016;28:651–6.
21 Manolio TA, Collins FS, Cox NJ, *et al*. Finding the missing heritability of complex diseases. *Nature* 2009;461:747–53.
22 Cortes A, Brown MA. Promise and pitfalls of the immunochip. *Arthritis Res Ther* 2011;13:101.
23 Ludvigsson JF, Andersson E, Ekbom A, *et al*. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;11:450.
24 Ekbom A. The Swedish multi-generation register. *Methods Mol Biol* 2011;675:215–20.
25 Ludvigsson JF, Almqvist C, Bonamy A-KE, *et al*. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol* 2016;31:125–36.
26 Lilleker JB, Vencovsky J, Wang G, *et al*. The EuroMyositis registry: an international collaborative tool to facilitate myositis research. *Ann Rheum Dis* 2018;77:30–9.
27 Svensson J, Arkema EV, Lundberg IE, *et al*. Incidence and prevalence of idiopathic inflammatory myopathies in Sweden: a nationwide population-based study. *Rheumatology* 2017;56:802–10.
28 Eriksson JK, Askling J, Arkema EV. The Swedish rheumatology quality register: optimisation of rheumatic disease assessments using register-enriched data. *Clin Exp Rheumatol* 2014;32:S-147–9.
29 Falconer DS. *Introduction to quantitative genetics. Introduction to quantitative genetics*, 1960.
30 Frisell T, Holmqvist M, Källberg H, *et al*. Familial risks and heritability of rheumatoid arthritis: role of rheumatoid factor/anti-citrullinated protein antibody status, number and type of affected relatives, sex, and age. *Arthritis Rheum* 2013;65:2773–82.
31 R Foundation for Statistical Computing. *R: A language and environment for statistical computing [program*. Vienna, Austria, 2020.
32 polycor: Polychoric and Polyserial Correlations [program]: R package version 0.7-10 2019.
33 Yang J, Lee SH, Goddard ME, *et al*. GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet* 2011;88:76–82.
34 Lee SH, Wray NR, Goddard ME, *et al*. Estimating missing heritability for disease from genome-wide association studies. *Am J Hum Genet* 2011;88:294–305.
35 Golan D, Lander ES, Rosset S. Measuring missing heritability: inferring the contribution of common variants. *Proc Natl Acad Sci U S A* 2014;111:E5272–81.
36 Moore DS, Shenk D. The heritability fallacy. *Wiley Interdiscip Rev Cogn Sci* 2017;8. doi:10.1002/wcs.1400. [Epub ahead of print: 01 12 2016].
37 Skov J, Eriksson D, Kuja-Halkola R, *et al*. Co-aggregation and heritability of organ-specific autoimmunity: a population-based twin study. *Eur J Endocrinol* 2020;182:473–80.
38 Kang EH, Go DJ, Mimori T, *et al*. Novel susceptibility alleles in HLA region for myositis and myositis specific autoantibodies in Korean patients. *Semin Arthritis Rheum* 2019;49:283–7.
39 Rothwell S, Chinoy H, Lamb JA. Genetics of idiopathic inflammatory myopathies: insights into disease pathogenesis. *Curr Opin Rheumatol* 2019;31:611–6.

CLINICAL SCIENCE

Treatment failure in giant cell arteritis

Sebastian H Unizony,[1] Min Bao,[2] Jian Han,[2] Yves Luder,[3] Andrey Pavlov,[4] John H Stone [1]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220347).

For numbered affiliations see end of article.

Correspondence to
Dr John H Stone, Vasculitis and Glomerulonephritis Center, Rheumatology, Immunology and Allergy Division, Massachusetts General Hospital, Boston, MA 02114, USA;
JHSTONE@mgh.harvard.edu

This work was presented, in part, at the 19th International Vasculitis and ANCA Workshop (Rheumatology, Volume 58, Issue Supplement_2, March 2019, kez063.082, https://doi.org/10.1093/rheumatology/kez063.082), the European League Against Rheumatism congress 2019 (http://dx.doi.org/10.1136/annrheumdis-2019-eular.2698) and the American College of Rheumatology congress 2019 (Arthritis Rheumatol. 2019; 71 (suppl 10). https://acrabstracts.org/abstract/risk-factors-for-treatment-failure-in-patients-with-giant-cell-arteritis-treated-with-tocilizumab-plus-prednisone-versus-prednisone-alone/).

Received 12 March 2021
Accepted 24 May 2021
Published Online First 28 May 2021

To cite: Unizony SH, Bao M, Han J, *et al*. *Ann Rheum Dis* 2021;**80**:1467–1474.

ABSTRACT

Objective Identify predictors of treatment failure in patients with giant cell arteritis (GCA) receiving tocilizumab in combination with glucocorticoids and in patients with GCA receiving only glucocorticoids.

Methods Posthoc analysis of the Giant-Cell Arteritis Actemra trial including 250 patients who received tocilizumab every week plus a 26-week prednisone taper (n=100), tocilizumab every-other-week plus a 26-week prednisone taper (n=49) or placebo plus a 26-week (n=50) or 52-week (n=51) prednisone taper in the intention-to-treat population. Responders for this analysis were patients who maintained remission (no GCA signs/symptoms and no erythrocyte sedimentation rate elevation) through week 52. Treatment failure was defined as inability to achieve remission by week 12 or relapse between weeks 12 and 52. Predictors investigated in univariate and multivariable analyses included patient characteristics, disease-related and treatment-related factors and patient-reported outcomes (PROs).

Results 149 patients received tocilizumab plus prednisone (TCZ/PDN) and 101 received placebo plus prednisone (PBO+PDN). After adjustment for confounders, treatment failure was significantly less likely in the TCZ/PDN group than the PBO/PDN group (OR, 0.2; 95% CI, 0.1 to 0.3; p<0.0001). Risk for treatment failure was significantly higher in women than men in the PBO/PDN group (OR, 5.2; 95% CI, 1.6 to 17.2; p=0.007) but not in the TCZ/PDN group. Predictors of treatment failure in the TCZ/PDN group included lower baseline prednisone doses and worse PROs at baseline.

Conclusion The strongest risk factors for treatment failure in GCA are treatment with prednisone alone and female sex. Lower starting prednisone doses and impaired PROs are associated with failure to respond to tocilizumab.

Trial registration number NCT01791153.

Key messages

What is already known about this subject?

- Most patients with giant cell arteritis (GCA) treated with glucocorticoids alone experience disease relapse and develop glucocorticoid-related toxicity, and up to 30% of patients experience relapse while receiving tocilizumab.
- Risk factors for treatment failure have been investigated in patients with GCA treated only with glucocorticoids. However, a consistent profile defining risk for relapse across studies was not observed and findings were discrepant. Virtually nothing is known about the determinants for relapse in patients with GCA treated with tocilizumab.

What does this study add?

- Our analyses demonstrated that patients with GCA receiving tocilizumab in combination with prednisone were six times less likely to experience treatment failure than those receiving prednisone alone.
- Female sex was the strongest risk factor for treatment failure in prednisone only-treated patients, whereas lower prednisone doses and worse patient-reported outcomes at study baseline increased the risk for treatment failure in patients treated with tocilizumab.

How might this impact on clinical practice or future developments?

- Given the absence of biomarkers to assess the risk for disease relapse in GCA, knowledge of epidemiological, clinical and treatment-related variables associated with poor disease outcomes could help clinicians better stratify, treat and monitor patients.
- Women experience treatment failure significantly more often than men when receiving glucocorticoids alone, and tocilizumab might mitigate this risk, whereas the discovery that patient-reported outcomes predicted treatment failure is a hypothesis generating finding that should be further explored in future studies.

INTRODUCTION

The clinical course of patients with giant cell arteritis (GCA) treated only with glucocorticoids has been complicated by high rates of disease relapse (40%–80% of patients)[1–4] and frequent glucocorticoid-related toxicity (>85% of cases).[3 5–7] Interleukin-6 (IL-6) blockade therapy with tocilizumab has improved the outcomes of patients with GCA by decreasing the risk for relapse, reducing the cumulative exposure to glucocorticoids and improving patients' health-related quality of life.[8–13] Nevertheless, tocilizumab treatment is not successful in all patients, and approximately 25%–30% of them experience relapse while receiving this medication.[4 11]

Several studies have explored factors associated with disease relapse in patients with GCA treated only with glucocorticoids.[3 14 15] Identified predictors for treatment failure have included sex,[14] clinical features at disease onset (eg, polymyalgia rheumatica (PMR) symptoms, strong systemic inflammatory response and weight loss),[3 16 17] certain

comorbidities (eg, diabetes)[14] and increased serum proinflammatory cytokine levels (IL-6 and tumour necrosis factor-α).[18] However, a consistent phenotype associated with treatment failure has not been identified, and results found in some studies have not always been replicated in others.

In contrast, virtually nothing is known about determinants for disease relapse in patients treated with tocilizumab. This problem, coupled with the unreliability of C reactive protein (CRP) levels and the erythrocyte sedimentation rate (ESR) for disease activity monitoring with IL-6 blockade therapy,[4 19] makes the longitudinal care of patients with GCA treated with tocilizumab challenging.

Risk stratification of patients with GCA based on clinical predictors may assist clinicians in choosing the most appropriate treatment and monitoring regimens for each case. We aimed to identify predictors of treatment failure in patients with GCA who received prednisone alone or tocilizumab plus prednisone.

METHODS

Study design and participants

We performed a posthoc analysis of data from the randomised, placebo-controlled Giant-Cell Arteritis Actemra (GiACTA) trial (ClinicalTrials.gov, NCT01791153)[8] to identify predictors of treatment failure because of refractory disease (failure to achieve disease remission over the first 12 weeks) or disease relapse following remission in patients with GCA. Details of the trial design have been published.[20] The trial was conducted at 76 centres in 14 countries (see online supplemental appendix 1 for list of investigators). Patients with active disease within 6 weeks of baseline were randomly assigned in a 2:1:1:1 ratio to one of four treatment arms: tocilizumab 162 mg subcutaneously every week plus a 26-week prednisone taper (n=100); tocilizumab 162 mg subcutaneously every other week plus a 26-week prednisone taper (n=50); placebo plus a 26-week prednisone taper (n=50) and placebo plus a 52-week prednisone taper (n=51). The intention-to-treat population consisted of 250 patients because one patient who had been assigned to receive tocilizumab every other week did not receive the trial drug and was excluded from the analysis. For this analysis, the two tocilizumab plus prednisone arms were combined (TCZ/PDN group) and the two placebo plus prednisone arms were combined (PBO/PDN group).

Either glucocorticoid treatment for GCA was initiated or the previously used dose was maintained or modified during screening at the discretion of the investigators. At baseline, patients had to be receiving a daily prednisone dose between 20 mg and 60 mg. From baseline through week 52, the prednisone dose was tapered as determined by the protocol.

Randomisation was performed using an interactive voice response system and was stratified according to whether each patient's baseline prednisone dose was ≤30 or >30 mg/day. Patients were randomly assigned to receive tocilizumab or matching placebo by subcutaneous injection. Prednisone doses between 60 mg and 20 mg were administered open-label, and doses below 20 mg were provided in weekly blister packs for blinded administration with marked daily doses that included prednisone or placebo capsules.

The GiACTA trial was approved by institutional review boards at the institutions involved and was conducted under the guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

Outcome definitions and predictors

Treatment response was defined as the achievement and maintenance of clinical remission from week 12 to week 52 with adherence to the protocol prednisone taper. Clinical remission status was determined by the investigators based on the absence of disease activity, defined as GCA signs and symptoms or ESR elevation attributable to GCA that required treatment intensification. The requirement for normalisation of CRP levels to <1 mg/dL, which was part of the definition of remission for the primary analysis,[8] was not included in the definition of clinical remission for the current analysis. Treatment failure was defined as failure to achieve clinical remission by week 12 (refractory disease) or relapse of disease activity between week 12 and week 52 after the achievement of clinical remission by week 12.

Potential predictors of treatment failure included demographic and patient characteristics, disease features (eg, new-onset vs relapsing disease, duration of disease, clinical manifestations and levels of inflammatory markers), treatment-related factors (TCZ/PDN vs PBO/PDN treatment group and initial prednisone dose) and patient-reported outcomes (PROs) (online supplemental box 1). The PROs evaluated were Patient Global Assessment of Disease Activity (PtGA) score,[21] Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale,[22] 36-Item Short Form Survey (SF-36)[23] and EuroQol-5D (EQ-5D) score[24] (online supplemental table 1). Except for data on clinical manifestations that reflected the time of disease presentation (ie, headache, scalp tenderness, jaw claudication, GCA-related visual loss, PMR symptoms, positive temporal artery biopsy and imaging demonstrating large-vessel vasculitis), all other predictor variables were measured at baseline.

Statistical analysis

All analyses were performed using SAS statistical software. Continuous data were described as means and SD or medians and IQR, and categorical variables were described as absolute frequencies and percentages. The Cochran-Mantel-Haenszel test was used to compare the proportions of patients who experienced treatment failure between the PBO/PDN group and the TCZ/PDN group adjusted for baseline prednisone dose (≤30 mg/day or >30 mg/day). Univariate and multivariable analyses were performed to identify predictors of treatment failure in the entire cohort of patients as well as in the TCZ/PDN and PBO/PDN groups separately. Variables considered for the analyses were initially selected based on current understanding of risk factors for poor treatment outcomes in GCA. Univariate comparisons were made using *t* tests and χ^2 tests for continuous and categorical data, respectively. Logistic regression was used for multivariable analyses and included treatment group and a set of variables chosen based on scientific rationale (new-onset vs relapsing disease, duration of disease, prednisone dose at baseline). Additionally, variables associated with treatment failure in univariate analyses of the entire cohort ($p<0.05$) were entered in the multivariable models. Multicollinearity was examined using the variance inflation factors. PROs exhibited a high degree of collinearity and therefore were not allowed to enter a logistic regression model simultaneously. Results of the multivariable analyses were reported as estimated ORs for treatment failure, with corresponding 95% CI. All analyses were exploratory, and no adjustment was made for type I error control.

RESULTS

Baseline characteristics of patients in the GiACTA trial cohort[25] and the primary analysis[8] are published. The 250 patients

Table 1 Baseline characteristics of patients with GCA who met criteria for treatment response or failure

	PBO/PDN* (n=94)	TCZ/PDN* (n=130)	All patients* (n=224)
Age, years	68.4 (7.7)	68.9 (8.4)	68.7 (8.1)
Female, n (%)	71.0 (75.5)	98.0 (75.4)	169.0 (75.4)
GCA duration, weeks	43.7 (73.6)	41.9 (78.9)	42.7 (76.6)
Newly diagnosed disease, n (%)	45.0 (47.9)	66.0 (50.8)	111.0 (49.6)
Cranial symptoms only or cranial and PMR symptoms, n (%)	75.0 (79.8)	103.0 (79.2)	178.0 (79.5)
PMR symptoms only, n (%)	19.0 (20.2)	27.0 (20.8)	46.0 (20.5)
Cranial symptoms only, n (%)	33.0 (35.1)	51.0 (39.2)	84.0 (37.5)
Baseline prednisone dose, mg/day, n (%)	35.2 (13.7)	35.7 (13.3)	35.5 (13.4)
Baseline prednisone dose ≤30 mg/day, n (%)	48.0 (51.1)	64.0 (49.2)	112.0 (50.0)
CRP, mg/L	8.0 (16.9)	8.2 (17.0)	8.1 (16.9)
ESR, mm/hour	25.6 (21.4)	23.2 (17.7)	24.2 (19.4)
PtGA, 100 mm VAS	41.4 (28.2)	43.9 (25.6)	42.8 (26.7)
EQ-5D score	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)
FACIT-Fatigue score	33.8 (13.4)	36.5 (11.2)	35.4 (12.2)
SF-36 MCS	41.7 (13.4)	44.7 (12.8)	43.4 (13.1)
SF-36 PCS	42.5 (10.0)	42.8 (8.6)	42.7 (9.2)

Data are shown as mean (SD) unless specified otherwise.
*Does not include the 26 patients (seven TCZ/PDN, 19 PBO/PDN) who were non-responders for reasons other than treatment failure (see supplementary table 2) for reasons for non-response in this group).
CRP, C reactive protein; EQ-5D, EuroQol 5-D; ESR, erythrocyte sedimentation rate; FACIT, Functional Assessment of Chronic Illness Therapy; GCA, giant cell arteritis; MCS, Mental Component Summary; PBO/PDN, placebo+prednisone; PCS, Physical Component Summary; PMR, polymyalgia rheumatica; PtGA, Patient Global Assessment of Disease Activity; SF-36, 36-Item Short Form Survey; TCZ/PDN, tocilizumab+prednisone; VAS, visual analogue scale.

included in the intention-to-treat analysis (101 in the PBO/PDN group and 149 in the TCZ/PDN group) were 113 treatment responders (45.2%) at week 52, 111 non-responders because of treatment failure (44.4%) (refractory disease or disease relapse) and 26 non-responders because of other reasons (10.4%) (online supplemental table 2). Table 1 depicts the baseline characteristics of the 224 patients (TCZ/PDN, n=130; PBO/PDN, n=94) defined as treatment responders or treatment failures, excluding the 26 classified as non-responders for reasons other than treatment failure.

Risk for treatment failure

Treatment regimen was the strongest predictor of treatment failure. Treatment response was achieved by 86 patients (66.2%) in the TCZ/PDN group and 27 patients (28.7%) in the PBO/PDN group (table 2). Accordingly, rates of treatment failure were significantly lower in the TCZ/PDN group than the PBO/PDN group (33.8% vs 71.3%; p<0.0001). In multivariable logistic regression adjusting for disease duration, baseline prednisone dose, previous disease relapse and sex, the OR for treatment failure in the TCZ/PDN group versus the PBO/PDN group was 0.2 (95% CI, 0.1 to 0.3; p<0.0001) (figure 1A). In addition, in the TCZ/PDN group, patients receiving ≤30 mg prednisone/day at baseline were at higher risk for treatment failure than those receiving >30 mg/day (OR 2.4; 95% CI, 1.0 to 5.9; p=0.046) (figure 1B). However, baseline prednisone dose did not predict treatment failure in patients in the PBO/PDN group (figure 1C).

Table 2 Rates of treatment response and treatment failure

	PBO/PDN (n=94)	TCZ/PDN (n=130)	P value*
Treatment response, n (%)	27 (28.7)	86 (66.2)	
Treatment failure, n (%)	67 (71.3)	44 (33.8)	<0.0001
Refractory disease	31 (33.0)	18 (13.8)	
Disease relapse	36 (38.3)	26 (20.0)	

*Cochran-Mantel-Haenszel test comparing the proportions of patients with treatment failure between the PBO/PDN group and the TCZ/PDN group adjusted for baseline prednisone dose (≤30 mg/day or >30 mg/day).
PBO/PDN, placebo+prednisone; TCZ/PDN, tocilizumab+prednisone.

In unadjusted analysis of the entire cohort, women accounted for 85.6% of the treatment failures and 65.5% of the treatment responses (p=0.0005; table 3). When the analysis was limited to each treatment group, results showed that among PBO/PDN-treated patients, women were significantly over-represented in the treatment failure group and under-represented in the treatment response group (86.6% vs 48.1%; p<0.0001; table 4), but a difference in outcome according to sex was not observed in TCZ/PDN-treated patients. Multivariable analysis confirmed female sex as an independent risk factor for treatment failure among PBO/PDN recipients (OR 5.5; 95% CI 1.6 to 18.7; p=0.006) but not among TCZ/PDN recipients (OR 2.3; 95% CI 0.8 to 6.7; p=0.12; Figure 1B,C). Age, race and body mass index were not associated with treatment outcome (tables 3 and 4).

Disease-related features as predictors of treatment failure

Jaw claudication and PMR symptoms at GCA diagnosis were associated with treatment failure in univariate and multivariable analyses of the entire cohort (table 3, figure 1A). When each treatment group was analysed separately, however, only jaw claudication came close to achieving statistical significance as a clinical feature that independently predicted treatment failure among the TCZ/PDN-treated patients (OR 2.3; 95% CI 1.0 to 5.5; p=0.06) (figure 1B). In contrast, no clinical manifestations independently predicted treatment failure in the PBO/PDN group (figure 1C). Moreover, there were no significant differences in treatment outcome associated with duration of disease, disease type (new-onset vs relapsing disease), baseline level of ESR and CRP or presence of large vessel vasculitis identified by imaging at the time of GCA diagnosis (all p>0.05; tables 3 and 4; figure 1).

Relationship between PROs and treatment failure

Univariate analyses showed that lower baseline health-related quality of life and increased baseline patient perception of disease activity were associated with treatment outcome. In analyses of the entire cohort (table 3), PtGA scores were significantly higher (ie, worse) in patients who experienced treatment failure (p=0.012). Accordingly, these patients had significantly lower (ie, worse) FACIT-Fatigue (p<0.0001), SF-36 Physical Component Summary (PCS) (p=0.0002), SF-36 Mental Component Summary (MCS) (p=0.0023) and EQ-5D (p=0.0064) scores. When treatment groups were analysed separately (table 4), a statistically significant association was found between PROs and treatment failure for all PROs (p<0.05) except PtGA (p=0.46) and EQ-5D (p=0.14) in PBO/PDN-treated patients and SF-36 MCS (p=0.11) in TCZ/PDN-treated patients.

To explore the independent effect of PROs on treatment outcome while avoiding the problem of collinearity associated with these tools, we constructed logistic regression models that included one PRO at a time. Covariates included in the models were treatment group (TCZ/PDN vs PBO/PDN), baseline prednisone dose, sex, duration of disease, new-onset versus relapsing disease at baseline, PMR and jaw claudication. Baseline PROs independently predicted treatment failure among TCZ/PDN-treated patients but not among PBO/PDN-treated patients

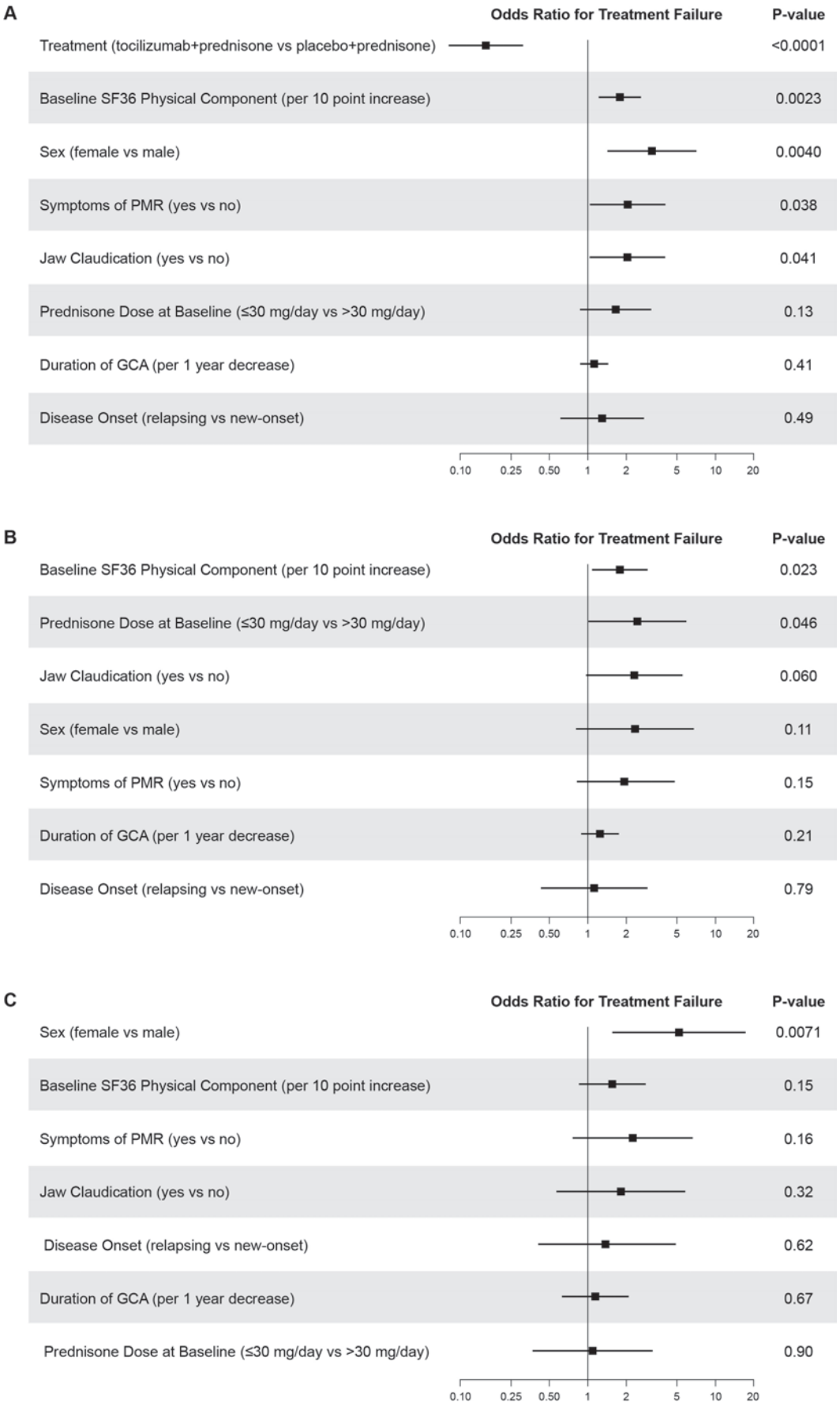


Figure 1 Multivariable analysis of treatment failure (PRO SF-36 Physical Component Summary) for the (A) entire cohort, (B) tocilizumab+prednisone group and (C) placebo+prednisone group. GCA, giant cell arteritis; PMR, polymyalgia rheumatica; PRO, patient-reported outcome; SF-36, 36-Item Short Form Survey.

Table 3 Univariate analysis of treatment failure (intention-to-treat population with treatment outcome defined)

Characteristic	Treatment response (n=113)	Treatment failure (n=111)	P value
Patient-related features			
Age, years, mean (SD)	68.4 (8.3)	68.9 (7.9)	0.64
Female sex, n (%)	74 (65.5)	95 (85.6)	0.00051
White, n (%)	110 (97.3)	109 (98.2)	0.51
BMI, mean (SD)	26.1 (4.3)	25.7 (4.5)	0.52
Disease-related features			
At the time of GCA diagnosis, n (%)			
Headaches	83 (73.5)	70 (63.1)	0.095
Scalp tenderness	40 (35.4)	38 (34.2)	0.85
Jaw claudication	30 (26.5)	44 (39.6)	0.037
GCA-related vision loss	8 (7.1)	10 (9.0)	0.60
PMR symptoms	62 (54.9)	78 (70.3)	0.017
Positive temporal artery biopsy	66/76 (86.8)	71/76 (93.4)	0.17
Imaging demonstrating LVV	56/62 (90.3)	50/61 (82.0)	0.18
At study baseline			
New-onset disease, n (%)	61 (54)	50 (45)	0.18
GCA duration, weeks, mean (SD)	37.9 (75.1)	47.5 (78.1)	0.35
ESR, mm/hour, mean (SD)	22.5 (17.9)	26.0 (20.7)	0.18
CRP, mg/dL, mean (SD)	6.6 (11.2)	9.7 (21.2)	0.17
Treatment-related features			
Baseline prednisone dose, mg/day, mean (SD)	36.0 (13.4)	34.9 (13.5)	0.56
Patient-reported outcomes			
PtGA, mm, mean (SD)	38.4 (26.8)	47.4 (25.9)	0.012
FACIT-Fatigue scale, mean (SD)	39.0 (10.6)	31.7 (12.7)	<0.0001
SF-36 PCS, mean (SD)	44.9 (8.5)	40.4 (9.3)	0.00021
SF-36 MCS, mean (SD)	46.0 (11.8)	40.7 (13.9)	0.0023
EQ-5D score, mean (SD)	0.8 (0.2)	0.7 (0.2)	0.0064

BMI, body mass index; CRP, C reactive protein; EQ-5D, EuroQol-5D; ESR, erythrocyte sedimentation rate; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue scale; GCA, giant cell arteritis; LVV, large vessel vasculitis; MCS, Mental Component Summary; PCS, Physical Component Summary; PMR, polymyalgia rheumatica; PtGA, Patient Global Assessment of Disease Activity; SF-36, 36-Item Short Form Survey.

(table 5, figure 1). In the TCZ/PDN group, SF-36 PCS and FACIT-Fatigue demonstrated relatively larger effects on treatment outcome with ORs for treatment failure of 1.8 (95% CI 1.1 to 2.9; p=0.02) and 1.8 (95% CI 1.2 to 2.6; p=0.002), respectively, for every 10-point decrease in a score at baseline (table 5, figure 1B).

DISCUSSION

Treatment failure has major implications for patients with GCA because of disease-associated morbidity and because of the need for additional glucocorticoid therapy, which nearly always leads to treatment-induced toxicity.[3 5–7 26] The absence of reliable biomarkers to monitor disease activity[1 4] and to predict treatment failure poses a significant challenge in GCA management. Our analysis identified independent predictors of treatment failure in GCA. These include the use of glucocorticoid monotherapy in general. In addition, a sharp disparity between women and men was observed among patients treated with prednisone alone: women had a strikingly higher risk for treatment failure, reflected by an OR of 5.2. Among patients randomly assigned to tocilizumab-based regimens, lower initial prednisone doses and worse PROs were significant predictors of treatment failure.

Few studies have explored factors associated with relapse in patients receiving glucocorticoids alone,[3 14 15] but the identification of a consistent phenotype associated with treatment failure has been elusive. Predictors previously identified include sex,[14] clinical features at disease onset (eg, PMR symptoms and significant weight loss),[3 16 17] certain comorbidities (eg, diabetes)[14] and increased serum IL-6 levels.[18] Our findings confirm that female sex is a major risk factor for GCA—the disease occurs three times more frequently in women than in men—and a predictor of disease severity.[14 27 28] We observed that the risk for treatment failure was fivefold higher in women receiving prednisone alone, but the differential response according to sex did not reach statistical significance in women assigned to tocilizumab. Comparison of the risk for treatment failure in women and men assigned to tocilizumab fell short of statistical significance, yet the OR for treatment failure among women was 2.3. These disparities in outcomes defined by sex are noteworthy because, on a per kilogram basis, women received more therapy—glucocorticoids and tocilizumab—than men. Thus, although IL-6 signalling blockade therapy represents a major advance for patients with GCA in general and an important step forward for women with this disease, a crucial unanswered question is why women with GCA are more likely to experience treatment failure with current regimens, particularly glucocorticoids. The finding is not dissimilar to the fact that women are at greater risk for many immune-mediated conditions, such as systemic lupus erythematosus, and that they often have more severe disease courses than men. The basis for these differences in disease expression across the sexes is, in fact, one of the central mysteries of rheumatic disease. In GCA, between-sex genetic differences localised to the X chromosome, the role of sex hormones (although GCA generally occurs in the postmenopausal population) and differences in body composition between women and men are all worthy of further investigation.

Although the introduction of tocilizumab has altered the standard of care for GCA,[8 9] treatment failure attributed to refractory disease or disease relapse occurs in nearly 30% of patients, which may indicate that inflammatory pathways independent from IL-6 can predominate in some cases. No studies have addressed the risk factors for disease flare among tocilizumab-treated patients. After adjusting for potential confounders, we quantified the therapeutic effect of tocilizumab and observed that its use decreased the risk for treatment failure by approximately fivefold compared with treatment regimens containing prednisone alone. In addition, among patients receiving tocilizumab, baseline prednisone doses lower than 30 mg/day were associated with decreased likelihood of long-term disease control, possibly because in tocilizumab-treated patients starting on higher doses of prednisone, the prednisone tapering schedule dictated that a longer time was needed to reach low prednisone doses, when the risk for flare begins to rise substantially. This longer interval probably permitted more time for the downstream effects of tocilizumab to be fully realised.

In contrast, similar to observations in other studies,[2 14 16 29] we found no association between treatment outcome and initial glucocorticoid dose in patients treated with prednisone alone. This suggests that the risk for relapse in patients treated with prednisone alone is determined less by the duration of the glucocorticoid taper than by the dose of prednisone a patient is

Table 4 Univariate analysis of treatment failure according to treatment (intention-to-treat population with treatment outcome defined)

	TCZ/PDN response (n=86)	TCZ/PDN failure (n=44)	P value	PBO/PDN response (n=27)	PBO/PDN failure (n=67)	P value
Patient-related features						
Age, years, mean (SD)	68.7 (8.2)	69.2 (8.8)	0.79	67.4 (8.4)	68.8 (7.4)	0.43
Female sex, n (%)	61 (70.9)	37 (84.1)	0.99	13 (48.1)	58 (86.6)	<0.0001
White, n (%)	84 (97.7)	43 (97.7)	0.29	26 (96.3)	66 (98.5)	0.50
BMI, mean (SD)	26.1 (4.4)	25.7 (4.9)	0.66	26.0 (4.1)	25.7 (4.3)	0.72
Disease-related features						
At the time of GCA diagnosis, n (%)						
Headaches	65 (75.6)	28 (63.6)	0.15	18 (66.7)	42 (62.7)	0.72
Scalp tenderness	30 (34.9)	18 (40.9)	0.50	10 (37.0)	20 (29.9)	0.50
Jaw claudication	24 (27.9)	18 (40.9)	0.13	6 (22.2)	26 (38.8)	0.12
GCA-related vision loss	5 (5.8)	4 (9.1)	0.49	3 (11.1)	6 (9.0)	0.75
PMR symptoms	48 (55.8)	31 (70.5)	0.11	14 (51.9)	47 (70.1)	0.093
Positive temporal artery biopsy	50/59 (84.7)	27/27 (100.0)	0.032	16/17 (94.1)	44/49 (89.8)	0.59
Imaging demonstrating LVV	44/49 (89.8)	21/25 (84.0)	0.47	12/13 (92.3)	29/36 (80.6)	0.33
At study baseline						
New-onset disease, n (%)	45 (52.3)	21 (47.7)	0.62	16 (59.3)	29 (43.3)	0.16
GCA duration, weeks, mean (SD)	42.4 (80.8)	40.9 (76.0)	0.92	23.6 (51.2)	51.8 (79.8)	0.093
ESR, mm/hour, mean (SD)	23.6 (18.3)	22.6 (16.7)	0.77	19.1 (16.3)	28.2 (22.7)	0.063
CRP, mg/dL, mean (SD)	6.9 (12.1)	10.9 (23.7)	0.21	5.7 (7.4)	9.0 (19.5)	0.40
Treatment-related features						
Baseline prednisone dose, mg/day, mean (SD)	36.3 (12.9)	34.3 (14.2)	0.42	34.8 (15.2)	35.3 (13.1)	0.88
Patient-reported outcomes						
PtGA: mm, mean (SD)	38.6 (26.4)	54.3 (20.5)	0.0008	38.0 (28.8)	42.8 (28.1)	0.46
FACIT-Fatigue scale, mean (SD)	38.8 (10.8)	32.0 (10.7)	0.0008	39.4 (10.2)	31.6 (13.9)	0.011
SF-36 PCS, mean (SD)	44.2 (8.4)	39.9 (8.3)	0.0076	47.2 (8.7)	40.7 (9.9)	0.0044
SF-36 MCS, mean (SD)	46.0 (11.7)	42.1 (14.6)	0.11	46.4 (12.4)	39.8 (13.4)	0.033
EQ-5D score, mean (SD)	0.8 (0.2)	0.7 (0.2)	0.027	0.8 (0.2)	0.7 (0.2)	0.14

BMI, body mass index; CRP, C reactive protein; EQ-5D, EuroQol-5D; ESR, erythrocyte sedimentation rate; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue scale; LVV, large vessel vasculitis; MCS, Mental Component Summary; PBO/PDN, placebo+prednisone; PCS, Physical Component Summary; PMR, polymyalgia rheumatica; PtGA, Patient Global Assessment of Disease Activity; SF-36, 36-Item Short Form Survey; TCZ/PDN, tocilizumab+prednisone.

receiving at a particular time. Stated another way, once prednisone is tapered to a certain daily dose (ie, a threshold), the risk for relapse increases, regardless of how long it takes for that dose level to be reached in a patient. Maintaining each patient at a prednisone dose above the flare threshold is likely to reduce the risk for relapse but can cause glucocorticoid toxicity to accumulate if that threshold is sufficiently high. One practical effect of tocilizumab appears to be lowering the prednisone threshold at which GCA flare is likely to occur.

We identified that PROs measuring functional health, well-being and subjective perception of disease activity were independently associated with treatment failure in tocilizumab-treated patients. Why PROs at baseline predicted treatment outcome only in the tocilizumab group is not entirely clear. IL-6 signalling is involved in the pathogenesis of sarcopaenia and frailty,[30 31] which can contribute to fatigue and other manifestations captured by the PRO instruments used in this study. We hypothesise that impaired health-related quality of life in GCA could reflect higher IL-6 levels that are not fully suppressed by IL-6 signalling blockade once glucocorticoids have been discontinued. Baseline PROs were measured for most patients when they were receiving high doses of prednisone to control their disease activity before they enrolled in GiACTA. It seems logical, therefore, that patients whose PRO scores were impaired despite high-dose prednisone treatment would be at greater risk for treatment failure during the trial. In contrast, because most patients receiving only glucocorticoids during the trial experienced treatment failure, PROs could not discriminate between two putative IL-6 states. Additionally, low statistical power attributed to the small sample size of the PBO/PDN group may, in part, explain the lack of association between PRO measures and treatment failure in patients receiving prednisone alone. The association between PRO scores and increased risk for treatment failure in tocilizumab-treated patients might also be driven by other disease mechanism pathways independently of IL-6.

Our study has certain limitations. First, it was a posthoc analysis of data from a clinical trial that was not specifically powered for the comparisons of interest. Second, because the two groups assessed in this exploratory analysis were different from those originally randomly assigned, bias from unevenly distributed unknown covariates could have been introduced. Nevertheless, our multivariable analyses accounted for the most important known confounders. Finally, the urgency with which GCA must be treated to prevent blindness precluded the collection of samples from patients with untreated active disease to measure inflammatory markers, including IL-6 levels. In fact,

Table 5 Multivariable analysis of PRO measures as predictors of treatment failure

	OR	95% CI	P value
SF-36 PCS (per 10-point decrease)			
All patients	1.8	1.2 to 2.6	0.0023
TCZ/PDN group	1.8	1.1 to 2.9	0.023
PBO/PDN group	1.6	0.9 to 2.8	0.15
FACIT-Fatigue scale (per 10-point decrease)			
All patients	1.6	1.2 to 2.2	0.00081
TCZ/PDN group	1.8	1.2 to 2.6	0.0028
PBO/PDN group	1.3	0.8 to 2.1	0.27
PtGA (per 10-point increase)			
All patients	1.2	1.0 to 1.3	0.028
TCZ/PDN group	1.3	1.1 to 1.5	0.0078
PBO/PDN group	1.0	0.8 to 1.2	0.99
SF-36 MCS (per 10-point decrease)			
All patients	1.3	1.0 to 1.7	0.040
TCZ/PDN group	1.3	1.0 to 1.8	0.090
PBO/PDN group	1.2	0.8 to 1.9	0.42
EQ-5D score (per 0.1-point decrease)			
All patients	1.2	1.0 to 1.4	0.063
TCZ/PDN group	1.2	1.0 to 1.5	0.038
PBO/PDN group	1.0	0.8 to 1.3	0.85

Each model included a single PRO and the following predictor variables: duration of disease at baseline, prednisone dose at baseline, new-onset vs relapsing disease at baseline, sex, PMR symptoms at GCA diagnosis, jaw claudication at GCA diagnosis and (for analysis of all patients) PBO/PDN vs TCZ/PDN treatment.
EQ-5D, EuroQol-5D; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue scale; GCA, giant cell arteritis; MCS, Mental Component Summary; PBO/PDN, placebo+prednisone; PCS, physical component summary; PMR, polymyalgia rheumatica; PRO, patient-reported outcome; PtGA, Patient Global Assessment of Disease Activity; SF-36, 36-Item Short Form Survey; TCZ/PDN, tocilizumab+prednisone.

most patients were already in glucocorticoid-induced remission before the baseline visit.[4] Therefore, the key question of whether impaired PROs at baseline were directly related to stronger inflammatory responses or higher IL-6 levels could not be tested. Along those lines, the fact that nearly all patients in the trial were started on prednisone during the screening period or even before the screening period—a measure that was appropriate and necessary—means that our ability to analyse the relationship between the level of the inflammatory state as reflected in baseline acute-phase reactants was limited. Future studies might aim to target this question more specifically, though obtaining samples from large numbers of patients before glucocorticoid therapy begins is challenging because of the urgency with which treatment must be initiated in GCA.

Our study has several strengths. First, our results were derived from prospectively collected data from the largest randomised, double-blind, placebo-controlled clinical trial in GCA.[8] During the trial, the prednisone taper was standardised and prednisone doses lower than 20 mg/day were administered in a blinded manner to prevent bias.[32] Second, our definition of relapse aligns with that commonly used in clinical practice, which includes the presence of clinical signs or symptoms of GCA with or without increased ESR levels necessitating treatment.[3 14 17] Of note, most relapses in this study were diagnosed after the manifestation of clinical signs or symptoms, with or without concomitant ESR elevation, and only nine relapses were determined based on the presence of an isolated elevation in ESR. Third, this is the first study to analyse predictors of treatment failure in patients with GCA receiving tocilizumab-based regimens, which are becoming the standard of care in this disease and for which more research is needed.

In summary, we identified important risk factors for treatment failure in GCA, the two strongest of which are prednisone monotherapy and female sex. Future studies might focus on elucidating the reasons for the striking disparity between men and women in risk for treatment failure, and future clinical trials must analyse in detail the impact of sex on treatment outcome.

Author affiliations
[1]Vasculitis and Glomerulonephritis Center, Rheumatology, Immunology and Allergy Division, Massachusetts General Hospital, Boston, Massachusetts, USA
[2]Genentech Inc, South San Francisco, California, USA
[3]F Hoffmann-La Roche Ltd, Basel, Switzerland
[4]Everest Clinical Research, Markham, Ontario, Canada

Correction notice This article has been corrected since it published Online First. Figure 1 has been replaced.

Contributors Conceptualised and designed study: SHU, YL, JHS. Acquired data: SHU, MB, JHS. Analysed and interpreted data: SHU, MB, JH, YL, AP, JHS. Drafted manuscript: SHU, MB. Critically revised manuscript for important intellectual content: All authors. Approved submission of the manuscript for publication: All authors

Funding The study was funded by the sponsor, F Hoffmann-La Roche Ltd. The sponsor was involved in the study design and conduct, in the analysis, interpretation and reporting of data and in the decision to submit the manuscript for publication. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit the manuscript for publication.

Competing interests SHU has received research funding from Roche/Genentech. MB, JH and YL own stock in and are employees of F Hoffmann-La Roche Ltd. AP is an employee of Everest Clinical Research, which received payment from Genentech for the submitted work. JHS has received research funding from Roche/Genentech and consulting fees from Chugai and Roche/Genentech.

Patient consent for publication Not required.

Ethics approval The study was conducted under the guidelines for Good Clinical Practice and the Declaration of Helsinki and was approved by institutional review boards at the institutions involved. All patients provided written informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

ORCID iD
John H Stone http://orcid.org/0000-0001-6588-9435

REFERENCES

1 Kermani TA, Warrington KJ, Cuthbertson D, *et al*. Disease relapses among patients with giant cell arteritis: a prospective, longitudinal cohort study. *J Rheumatol* 2015;42:1213–7.
2 Martinez-Lado L, Calviño-Díaz C, Piñeiro A. Relapses and recurrences in giant cell arteritis: a population-based study of patients with biopsy-proven disease from northwestern Spain. *Medicine* 2011;90:186–93.

3 Alba MA, Garcia-Martinez A, Prieto-Gonzalez S. Relapses in patients with giant cell arteritis: prevalence, characteristics, and associated clinical findings in a longitudinally followed cohort of 106 patients. *Medicine* 2014;93:194–201.
4 Stone JH, Tuckwell K, Dimonaco S, *et al*. Glucocorticoid dosages and Acute-Phase reactant levels at giant cell arteritis flare in a randomized trial of tocilizumab. *Arthritis Rheumatol* 2019;71:1329–38.
5 Proven A, Gabriel SE, Orces C, *et al*. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. *Arthritis Rheum* 2003;49:703–8.
6 Petri H, Nevitt A, Sarsour K, *et al*. Incidence of giant cell arteritis and characteristics of patients: data-driven analysis of comorbidities. *Arthritis Care Res* 2015;67:390–5.
7 Wilson JC, Sarsour K, Collinson N, *et al*. Incidence of outcomes potentially associated with corticosteroid therapy in patients with giant cell arteritis. *Semin Arthritis Rheum* 2017;46:650–6.
8 Stone JH, Tuckwell K, Dimonaco S, *et al*. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med Overseas Ed* 2017;377:317–28.
9 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.
10 Calderón-Goercke M, Loricera J, Aldasoro V, *et al*. Tocilizumab in giant cell arteritis. observational, open-label multicenter study of 134 patients in clinical practice. *Semin Arthritis Rheum* 2019;49:126–35.
11 Unizony S, McCulley TJ, Spiera R, *et al*. Clinical outcomes of patients with giant cell arteritis treated with tocilizumab in real-world clinical practice: decreased incidence of new visual manifestations. *Arthritis Res Ther* 2021;23:8.
12 Hellmich B, Agueda A, Monti S. Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis* 2018;2020:19–30.
13 Strand V, Dimonaco S, Tuckwell K, *et al*. Health-Related quality of life in patients with giant cell arteritis treated with tocilizumab in a phase 3 randomised controlled trial. *Arthritis Res Ther* 2019;21:64.
14 Labarca C, Koster MJ, Crowson CS, *et al*. Predictors of relapse and treatment outcomes in biopsy-proven giant cell arteritis: a retrospective cohort study. *Rheumatology* 2016;55:347–56.
15 Sugihara T, Hasegawa H, Uchida HA, *et al*. Associated factors of poor treatment outcomes in patients with giant cell arteritis: clinical implication of large vessel lesions. *Arthritis Res Ther* 2020;22:72.
16 Restuccia G, Boiardi L, Cavazza A. Flares in biopsy-proven giant cell arteritis in northern Italy: characteristics and predictors in a long-term follow-up study. *Medicine*2016;95:e3524.
17 Hernández-Rodríguez J, García-Martínez A, Casademont J, *et al*. A strong initial systemic inflammatory response is associated with higher corticosteroid requirements and longer duration of therapy in patients with giant-cell arteritis. *Arthritis Care Res* 2002;47:29–35.
18 García-Martínez A, Hernández-Rodríguez J, Espígol-Frigolé G, *et al*. Clinical relevance of persistently elevated circulating cytokines (tumor necrosis factor α and interleukin-6) in the long-term followup of patients with giant cell arteritis. *Arthritis Care Res* 2010;62:835–41.
19 Unizony S, Arias-Urdaneta L, Miloslavsky E, *et al*. Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, Takayasu arteritis) and polymyalgia rheumatica. *Arthritis Care Res* 2012;64:1720–9.
20 Unizony SH, Dasgupta B, Fisheleva E, *et al*. Design of the tocilizumab in giant cell arteritis trial. *Int J Rheumatol* 2013;2013:1–10.
21 Nikiphorou E, Radner H, Chatzidionysiou K, *et al*. Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. *Arthritis Res Ther* 2016;18:251.
22 Yellen SB, Cella DF, Webster K, *et al*. Measuring fatigue and other anemia-related symptoms with the functional assessment of cancer therapy (FACT) measurement system. *J Pain Symptom Manage* 1997;13:63–74.
23 Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection. *Med Care* 1992;30:473–83.
24 EuroQol G, EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
25 Tuckwell K, Collinson N, Dimonaco S, *et al*. Newly diagnosed vs. relapsing giant cell arteritis: baseline data from the GiACTA trial. *Semin Arthritis Rheum* 2017;46:657–64.
26 Broder MS, Sarsour K, Chang E, *et al*. Corticosteroid-related adverse events in patients with giant cell arteritis: a claims-based analysis. *Semin Arthritis Rheum* 2016;46:246–52.
27 Narvaez J, Nolla-Solé JM, Valverde-García J, *et al*. Sex differences in temporal arteritis and polymyalgia rheumatica. *J Rheumatol* 2002;29:321–5.
28 Tsalapaki C, Lazarini A, Antonatou K. THU0310 frequency of relapses and treatment discontinuation during long-term follow-up of patients with giant cell arteritis. *Ann Rheum Dis* 2017;76:321.
29 Chevalet P, Barrier JH, Pottier P. A randomized, multicenter, controlled trial using intravenous pulses of methylprednisolone in the initial treatment of simple forms of giant cell arteritis: a one year followup study of 164 patients. *J Rheumatol* 2000;27:1484–91.
30 Soysal P, Stubbs B, Lucato P, *et al*. Inflammation and frailty in the elderly: a systematic review and meta-analysis. *Ageing Res Rev* 2016;31:1–8.
31 Wilson D, Jackson T, Sapey E, *et al*. Frailty and sarcopenia: the potential role of an aged immune system. *Ageing Res Rev* 2017;36:1–10.
32 Collinson N, Tuckwell K, Habeck F, *et al*. Development and implementation of a double-blind corticosteroid-tapering regimen for a clinical trial. *Int J Rheumatol* 2015;2015:1–6.

CLINICAL SCIENCE

Ultrasound halo sign as a potential monitoring tool for patients with giant cell arteritis: a prospective analysis

Cristina Ponte ,[1,2] Sara Monti ,[3,4] Carlo Alberto Scirè ,[5,6] Paolo Delvino ,[3] Nikita Khmelinskii,[1,2] Alessandra Milanesi,[3] Vítor Teixeira ,[1,7] Fabio Brandolino,[3] Fernando Saraiva,[1] Carlomaurizio Montecucco ,[3] João Eurico Fonseca ,[1,2] Wolfgang A Schmidt,[8] Raashid Ahmed Luqmani[9]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220306).

For numbered affiliations see end of article.

Correspondence to
Dr Sara Monti, Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Lombardia, Italy; sara.saramonti@gmail.com

CP and SM contributed equally.

Received 7 March 2021
Accepted 16 June 2021
Published Online First 2 July 2021

ABSTRACT

Objectives To assess the sensitivity to change of ultrasound halo features and their association with disease activity and glucocorticoid (GC) treatment in patients with newly diagnosed giant cell arteritis (GCA).

Methods Prospective study of patients with ultrasound-confirmed GCA who underwent serial ultrasound assessments of the temporal artery (TA) and axillary artery (AX) at fixed time points. The number of segments with halo and maximum halo intima–media thickness (IMT) was recorded. Time points in which >80% of patients were assessed were considered for analysis. Halo features at disease presentation and first relapse were compared.

Results 49 patients were assessed at 354 visits. Halo sensitivity to change was assessed at weeks 1, 3, 6, 12 and 24 and showed a significant standardised mean difference between all time points and baseline for the TA halo features but only after week 6 for the AX halo features. The number of TA segments with halo and sum and maximum TA halo IMT showed a significant correlation with erythrocyte sedimentation rate (0.41, 0.44 and 0.48), C reactive protein (0.34, 0.39 and 0.41), Birmingham Vasculitis Activity Score (0.29, 0.36 and 0.35) and GC cumulative dose (−0.34, −0.37 and −0.32); no significant correlation was found for the AX halo features. Halo sign was present in 94% of first disease relapses but with a lower mean number of segments with halo and sum of halo IMT compared with disease onset (2.93±1.59 mm vs 4.85±1.51 mm, p=0.0012; 2.01±1.13 mm vs 4.49±1.95 mm, p=0.0012).

Conclusions Ultrasound is a useful imaging tool to assess disease activity and response to treatment in patients with GCA.

Key messages

What is already known about this subject?

- Ultrasound of the temporal artery (TA) and axillary artery (AX) showing a non-compressible halo sign is recommended for confirming a suspected diagnosis of giant cell arteritis (GCA); however, its value for monitoring disease activity is still poorly understood.

What does this study add?

- This study prospectively demonstrated that the number of TA segments with halo sign, as well as the TA halo intima–media thickness (IMT), is sensitive to change during a 24-week period and correlates with disease activity markers and glucocorticoid (GC) cumulative dose. AX halo IMT only decreases after 6 weeks of follow-up, and AX halo features show no correlation with disease activity markers nor with GC treatment.
- Ultrasound is useful for detecting GCA relapses, with 94% of first relapses showing the presence of halo sign, all with an increased IMT in comparison to the previous ultrasound examination performed.

How might this impact on clinical practice or future developments?

- Ultrasound has proven to be a valuable monitoring tool for patients with GCA. Assessment of ultrasound-specific halo features, instead of the current binary presence/absence of halo sign in any arterial segment, should be used to evaluate disease activity and response to treatment in patients with GCA. Future clinical trials in GCA should study treatment effect on halo features as an outcome measure.
- Ultrasound may be a feasible alternative for monitoring patients treated with interleukin 6 inhibitors, in whom the traditional acute-phase reactants—erythrocyte sedimentation rate and C reactive protein—have very limited value.

INTRODUCTION

Giant cell arteritis (GCA) is the most common form of primary systemic vasculitis in patients aged ≥50 years, causing chronic inflammation of the large-sized and medium-sized arteries.[1] Treatment with high doses of glucocorticoids (GCs) should be initiated as early as possible to prevent severe ischaemic manifestations of the disease, such as visual loss.[2] However, the optimal duration of GC treatment has been reported to vary among patients, with disease relapses occurring in around half the cases once GCs are tapered.[3–13] Although this highlights that not all patients with GCA follow the same disease course, there are no valid biomarkers to assess response to therapy. Changes in the traditional acute-phase

To cite: Ponte C, Monti S, Scirè CA, *et al*. *Ann Rheum Dis* 2021;**80**:1475–1482.

reactants—erythrocyte sedimentation rate (ESR) and C reactive protein (CRP)—do not consistently reflect disease activity, are not GCA-specific and have limited value in assessing patients treated with interleukin (IL) 6 inhibitors such as tocilizumab.[14–16]

Ultrasound of the temporal artery (TA) and axillary artery (AX) showing a non-compressible, homogenous, hypoechoic wall thickening—deemed as the 'halo sign'—has already proven to be effective in diagnosing patients with GCA.[17–22] However, its role in assessing response to treatment is still poorly understood.[17 23]

In the current study, we prospectively evaluated the utility of the ultrasound halo sign in monitoring patients with GCA. We assessed the sensitivity to change of halo sign-specific features and their association with disease activity markers and GC treatment, as well as the ultrasound characteristics of patients with clinical relapse.

METHODS

Patients and data collection

Patients with newly diagnosed GCA were recruited from the rheumatology departments of two university hospitals from Lisbon, Portugal, and Pavia, Italy, into a prospective, observational cohort study—Prognosis of Temporal Arteritis Study—between March 2017 and November 2019. All patients had to fulfil the original 1990 or the modified American College of Rheumatology classification criteria for GCA,[24 25] have the presence of halo sign on the ultrasound of TA and/or AX and have not been on high doses of GCs (≥30 mg/day of prednisolone or equivalent) for more than 15 days (online supplemental table 1). Patients were assessed at baseline; weeks 1, 3, 6 and 12; and then every 3 months, following the 2010 British Society for Rheumatology (BSR) guidelines for the management of GCA.[26] Extra visits were scheduled for suspected relapses. Clinical, laboratory and ultrasonographic data were collected at each visit. Treatment was tailored according to each individual patient, with GC reduction regimens following the BSR and European League Against Rheumatism (EULAR) recommendations.[23 26] Relapse was defined as the recurrence of GCA-related symptoms or increased levels of acute-phase reactants (CRP ≥1 mg/dL and/or ESR ≥30 mm/hour) not otherwise explained and requiring GC increase.[27] Remission was defined as the absence of relapse with a prednisolone dose <30 mg/day. Data were collected using a predefined case report form (online supplemental image 1). This study was approved by the Lisbon Academic Medical Centre and University of Pavia Ethics Committee (references 08/17 and E 2016 0031606, respectively). All patients provided written informed consent before inclusion in the study.

Ultrasonography

Eight arterial territories of interest were systematically assessed in all time points: bilateral common superficial TA, parietal and frontal branches and AX. The presence or absence of halo sign and the maximum value of intima–media thickness (IMT) was recorded for all arterial segments. The IMT was measured in longitudinal view, in the single wall distal to the probe and at the area with greatest wall thickness. Patients were examined with a GE Healthcare LOGIQ E9 ultrasound machine in Portugal and with an Esaote MyLab Seven in Italy. The 8–18 MHz hockey stick probe and the 6–18 MHz probe (GE and Esaote machines, respectively) were used with the following settings: greyscale frequency of 18 MHz for TA and 13–18 MHz for AX, colour Doppler frequency of ≥6 MHz, pulse repetition frequency of 2.5–3.5 kHz for TA and 3–4 kHz for AX, colour box steering of 20° and gain adjusted to fill only the lumen.[28] All examinations were performed by a single expert sonographer in each centre (CP and SM) who had previously undergone the same ultrasound training[29] and have performed >300 vascular ultrasounds prior to this study.[30] Both sonographers are rheumatologists and were not blinded to the clinical data at disease diagnosis and follow-up, including in cases of relapse.

Statistical analysis

Data were summarised by mean±SD for continuous variables and percentages and frequencies for categorical variables. Sensitivity to change of the halo sign features was analysed using only time points in which at least 80% of patients were assessed and was calculated as standardised mean difference (SMD) for each time point separately. The statistical significance was calculated by one-sample t-test. Temporal variations were analysed graphically by mean difference with 95% CI. Association between the halo sign features at each time point included ESR, CRP, Birmingham Vasculitis Activity Score (BVAS) and number of days on GCs, and GC cumulative dose was assessed using Spearman's correlation coefficient, estimated by linear regression models on standardised variables. Logistic regression was used to determine the probability of being in remission for each unit increase (standardised) of the halo feature of interest. Differences in halo features between disease onset and first relapse were assessed in the whole cohort using the Wilcoxon signed-rank test. All the analyses were performed on complete data, without imputation, and the cut-off of $p<0.05$ was adopted for defining statistical significance. Data were analysed using Stata V.14.

RESULTS

Patient characteristics at disease presentation

A total of 49 patients (28 from Portugal and 21 from Italy) were included: 36 (73.5%) women, mean age 78.2±7.4 years old. Table 1 and online supplemental table 2 detail patient characteristics at baseline. Of note, 19/49 (38.8%) patients were referred to us by the ophthalmology department. Before undergoing ultrasound, patients were being treated with high doses of GCs for a mean of 2.5±4.4 days and had a mean cumulative prednisolone (or equivalent) dose of 927.3±1864.3 mg. A total of 17/49 (34.7%) patients required intravenous pulses of methylprednisolone (0.5–1 g/day for a maximum of 3 days) at disease onset, and 12/49 (24.5%) had been started on this treatment before undergoing ultrasound assessment. All patients had at least one arterial segment with halo sign at baseline ultrasound; 220 arterial segments with halo were recorded (201 TA and 19 AX segments). TA involvement was reported in 47 (95.9%) patients and AX involvement in 11 (22.4%); nine (18.4%) patients had both TA and AX involvement, and two (4.1%) patients had exclusive AX involvement (table 2).

Halo sensitivity to change during disease follow-up

During the study period, a total of 354 visits were recorded. Patients were prospectively evaluated with a mean of 7.2±3.8 visits during a mean of 307.5±241.8 days. Based on the frequency of available observations (ie, in which >80% of patients were assessed), the following time points were considered for the prospective analysis of different halo features: baseline and weeks 1, 3, 6, 12 and 24. A total of 250 assessment visits were included: 49 at baseline (47 for patients with TA involvement and 11 with AX involvement), 45 at week 1 (44 TA and eight AX), 41 at week 3 (40 TA and eight AX), 44 at week 6 (42

Table 1 Patient characteristics at baseline

	Patients (n=49)
Demographics	
Female sex; n (%)	36 (73.5)
Age (years); mean±SD	78.2±7.4
Time since symptom onset and diagnosis (days); mean±SD	72.3±76.7
Symptoms at disease onset; n (%)	
Constitutional symptoms (any)	34 (69.4)
Fever (≥38°C or 100.4°F)	12 (24.5)
Weight loss (≥2 kg)	30 (61.2)
Arthralgia/myalgia	22 (44.9)
New persistent headache	42 (85.7)
New onset of vision loss (partial or complete)	19 (38.8)
Jaw claudication	34 (69.4)
Tongue claudication	6 (12.2)
Scalp tenderness	21 (42.9)
New onset of PMR	30 (61.2)
Laboratory tests at disease onset; mean±SD	
ESR (mm/hour)	89.2±25.9
CRP (mg/dL)	6.6±4.6
Diagnostic/classification features; n (%)	
Fulfilled the 1990 ACR classification criteria[24]	47 (95.9)
Fulfilled the modified ACR classification criteria for GCA[25]	37 (75.5)
Positive TAB (performed in two patients)*	1/2 (50.0)
Positive PET-CT and/or CTA for LV involvement (performed in two patients)	2/2 (100.0)
Immunosuppressive treatment	
Number of patients on high doses of GCs†; n (%)	20 (40.8)
Number of days on high doses of GCs†; mean±SD	2.5±4.4
Cumulative prednisolone (or equivalent) dose (mg); mean±SD	927.3±1864.3
Previous treatment with intravenous methylprednisolone; n (%)	12 (24.5)
Previous treatment with DMARDs; n (%)	0 (0.0)
GCA subtype; n (%)	
Cranial GCA	47 (95.9)
LV-GCA	11 (22.4)
Exclusive cranial GCA	38 (77.6)
Exclusive LV-GCA	2 (4.1)

*Both TABs were performed before ultrasound assessment: in the patient with a positive result, only the distal part of the left frontal branch was removed in the procedure, allowing ultrasonographic evaluation of its proximal part; the case with a negative result belonged to a patient with exclusive LV-GCA, in which the whole left parietal branch was removed precluding ultrasonographic assessment of this segment.
†≥30 mg/day of prednisolone or equivalent (including intravenous methylprednisolone).
ACR, American College of Rheumatology; CRP, C reactive protein; CTA, CT angiography; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; GCA, giant cell arteritis; LV, large vessel; PET-CT, positron emission tomography–CT; PMR, polymyalgia rheumatica; TAB, temporal artery biopsy.

TA and 10 AX), 35 at week 12 (34 TA and seven AX) and 36 at week 24 (34 TA and six AX).

At week 24, 16/36 (44.4%) patients were reported to have a halo sign: 12/16 with TA involvement and 5/16 with AX involvement. In only 3/16 (18.8%) patients, disease relapse was simultaneously observed. Nevertheless, in all these three cases, an increase in the number of arterial segments with halo and halo size was observed in comparison to the previous visit recorded.

Regarding the halo sensitivity to change during follow-up, table 3 shows a significant SMD between all time points and baseline for the TA halo features (sum of arterial segments, sum of halo IMT and maximum halo IMT) but only after week 6 for the AX halo features (sum and maximum halo IMT). Figure 1 shows the mean variation (not standardised) of the sum of all segments with halo and the sum of halo IMT during follow-up,

Table 2 Ultrasound characteristics at baseline

	Patients (n=49)
TA halo; n (%)	47 (95.9)
AX halo; n (%)	11 (22.4)
TA halo with AX halo; n (%)	9 (18.4)
TA halo without AX halo; n (%)	38 (77.6)
AX halo without TA halo; n (%)	2 (4.1)
Number of arterial segments with halo; n (%)	
One segment	3 (6.1)
Two segments	9 (18.4)
Three segments	2 (4.1)
Four segments	9 (18.4)
Five segments	6 (12.2)
Six segments	15 (30.6)
Seven segments	3 (6.1)
Eight segments	2 (4.1)
Number of segments with halo; mean±SD	
All segments (49 patients)	4.5±1.9
TA segments (47 patients)	4.2±1.7
AX segments (11 patients)	1.7±0.5
Sum of halo IMT (mm); mean±SD	
All halos (49 patients)	3.96±2.24
TA halos (47 patients)	3.48±1.86
AX halos (11 patients)	2.81±1.15
Maximum halo IMT (mm); mean±SD	
All halos (49 patients)	1.12±0.46
TA halos (47 patients)	0.96±0.30
AX halos (11 patients)	1.67±0.44

AX, axillary artery; IMT, intima–media thickness; TA, temporal artery.

Table 3 Standardised mean difference of halo features between baseline and different time points

	Week 1	Week 3	Week 6	Week 12	Week 24
Number of arterial segments:					
Sum of all segments with halo (n=49 patients)	**−0.51**	**−0.78**	**−1.13**	**−1.69**	**−1.52**
Sum of TA segments with halo (n=47 patients)	**−0.49**	**−0.78**	**−1.18**	**−1.87**	**−1.69**
Sum of AX segments with halo (n=11 patients)	−0.35	-	−0.62	−0.73	−0.91
Halo thickness (mm)					
Sum of all halo IMT (mm) (n=49 patients)	**−0.98**	**−1.44**	**−1.37**	**−1.6**	**−1.48**
Sum of TA halo IMT (mm) (n=47 patients)	**−1.01**	**−1.55**	**−1.54**	**−1.81**	**−1.69**
Sum of AX halo IMT (mm) (n=11 patients)	−0.15	−0.45	−0.81	−0.84	−0.98
Maximum TA halo IMT (mm) (n=47 patients)	**−1.07**	**−1.32**	**−1.47**	**−1.91**	**−2.19**
Maximum AX halo IMT (mm) (n=11 patients)	−0.04	−0.29	**−0.94**	**−1.13**	−1.01

The standardised mean difference of interest is reported as negative values and in units of SD.
The magnitude of the change may be interpreted as follows: small(−0.50–0.20), medium (−0.80–0.50), large (−1.30–0.80) and very large (−∞–1.30). In bold the statistically significant results (p<0.05); n=n of patients at baseline.
Bold indicates statistically significant numbers.
AX, axillary artery; IMT, intima–media thickness; TA, temporal artery.

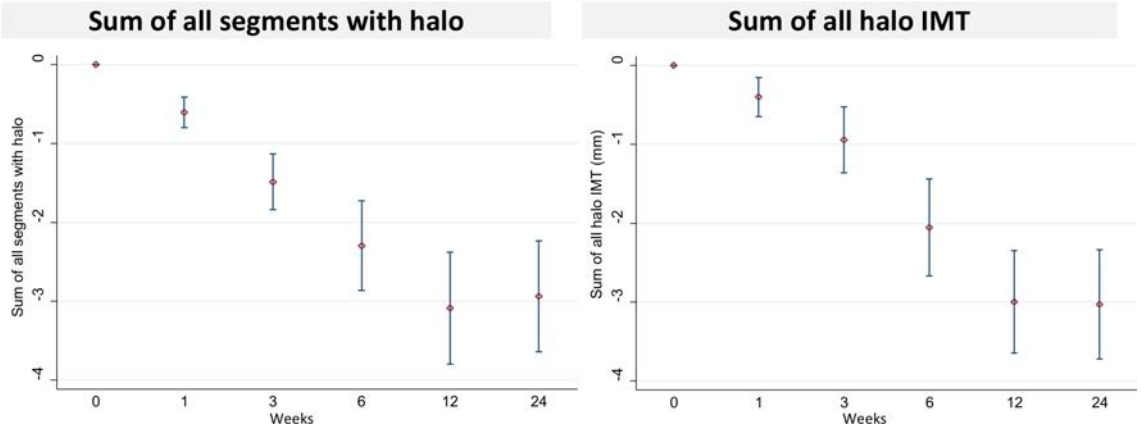


Figure 1 Mean variation (not standardised) of halo features at different time points. Mean variation (not standardised) of each halo feature is shown with 95% CI. Error bars crossing zero line indicate that the variation is not statistically significant at that particular time point. IMT, intima–media thickness.

with respective 95% CI. Figure 2 demonstrates the differences between TA and AX halo features. Figure 3 shows a clinical example of the difference in halo IMT reduction for TA and AX arteries between baseline and week 24.

Association between halo sign features and disease activity markers

During the 24-week follow-up, TA halo features showed a positive correlation with disease activity markers (ESR, CRP and BVAS); however, no significant correlation was found for the AX halo features (table 4). Of note, acute-phase reactants (CRP and ESR) that were increased due to other reasons than vasculitic activity (eg, infections) were excluded from this analysis. In addition, patients with smaller numbers of TA arterial segments with halo and lower values of TA halo IMT were more likely to achieve disease remission. By contrast, AX halo features showed no association with the likelihood of achieving disease remission.

Association between halo sign features and GC treatment

Patients assessed at week 24 had been treated with high doses of GCs for a mean of 65.0±42.9 days and had a mean cumulative prednisolone (or equivalent) dose of 6342.2±2373.0 mg. During the 24-week period of follow-up, a significant negative correlation was found between TA halo features (number of segments and IMT) and GC cumulative dose, but the same was not verified for the AX halo features (table 5). Moreover, no significant correlation was observed between the TA and AX halo features and number of days on high doses of GCs. A total of nine patients were started on disease-modifying antirheumatic drug (DMARD) treatment during this period: seven on methotrexate, one on tocilizumab and one on methotrexate followed by tocilizumab. Nevertheless, when the correlation between halo features and GC treatment was adjusted for DMARD treatment, no relevant differences were found (online supplemental table 3).

Halo features at disease relapse

During the whole study period, we observed 32 flares in 19 patients (38.8%). The mean time to first disease relapse was 31.8 weeks±18.5 days (median 36 weeks and IQR 12–48). In 17/19 cases of first relapse, an ultrasound was performed within 15 days of GC restart or increase in GC dose. One patient was not able to attend the ultrasound assessment and had to be managed remotely, and the other patient decided to increase the GC dose from 5 mg to 10 mg 1 month prior to being assessed by ultrasound. In 16/17 (94.1%) of the remaining relapses, at least one arterial segment was found to have a positive halo sign: 14/16 (87.5%) with TA halo and 3/16 (18.8%) with AX halo. In all 16 cases, an increase in halo IMT (sum and maximum), with or without an increase in the number of arterial segments with halo, was observed in comparison to the previous ultrasound assessment recorded. Table 6 presents the differences between halo features at baseline and first disease relapse for these patients. A lower number of segments with halo (all segments and TA segments) were reported for patients presenting with clinical relapse in comparison to their initial presentation. In addition, a diminished value of TA halo IMT (sum or maximum value) was observed in relapsing cases. Of note, the patient who was recorded as having a disease relapse, but no halo on ultrasound, only complained of symptoms suggestive of polymyalgia rheumatica.

DISCUSSION

Given the limitations of a monitoring approach in GCA just focused on the assessment of clinical symptoms, signs and laboratory markers, imaging techniques have emerged as promising tools to aid the evaluation of patients with GCA during their disease course.[31–33]

Most studies on the use of ultrasound as a potential monitoring tool[29 33–40] for GCA have been based on retrospective data[29 38–40] and used the presence or absence of halo sign to establish associations with clinical findings.[29 33 35 37 39 40] Specific halo features (eg, number of arterial segments with halo, involvement of AX and size of IMT)[41–45] have already been reported to increase the diagnostic performance of ultrasound in GCA, but their value has never been prospectively assessed for monitoring disease activity using various time points. Moreover, most follow-up studies lack the inclusion of ultrasound assessments within the first 2 weeks of treatment initiation,[33–35 37 40] although TA halo disappearance or substantial decrease may occur in the first week of GC treatment.[46–48]

We have demonstrated the utility of ultrasound, based on detecting the halo sign, to evaluate disease activity and response to treatment in patients with GCA in a 6-month prospective cohort. We found a significant change from baseline in all TA halo features assessed (sum of arterial segments with halo, sum of halo IMT and maximum halo IMT) during every visit included. Moreover, we observed a positive correlation of low magnitude

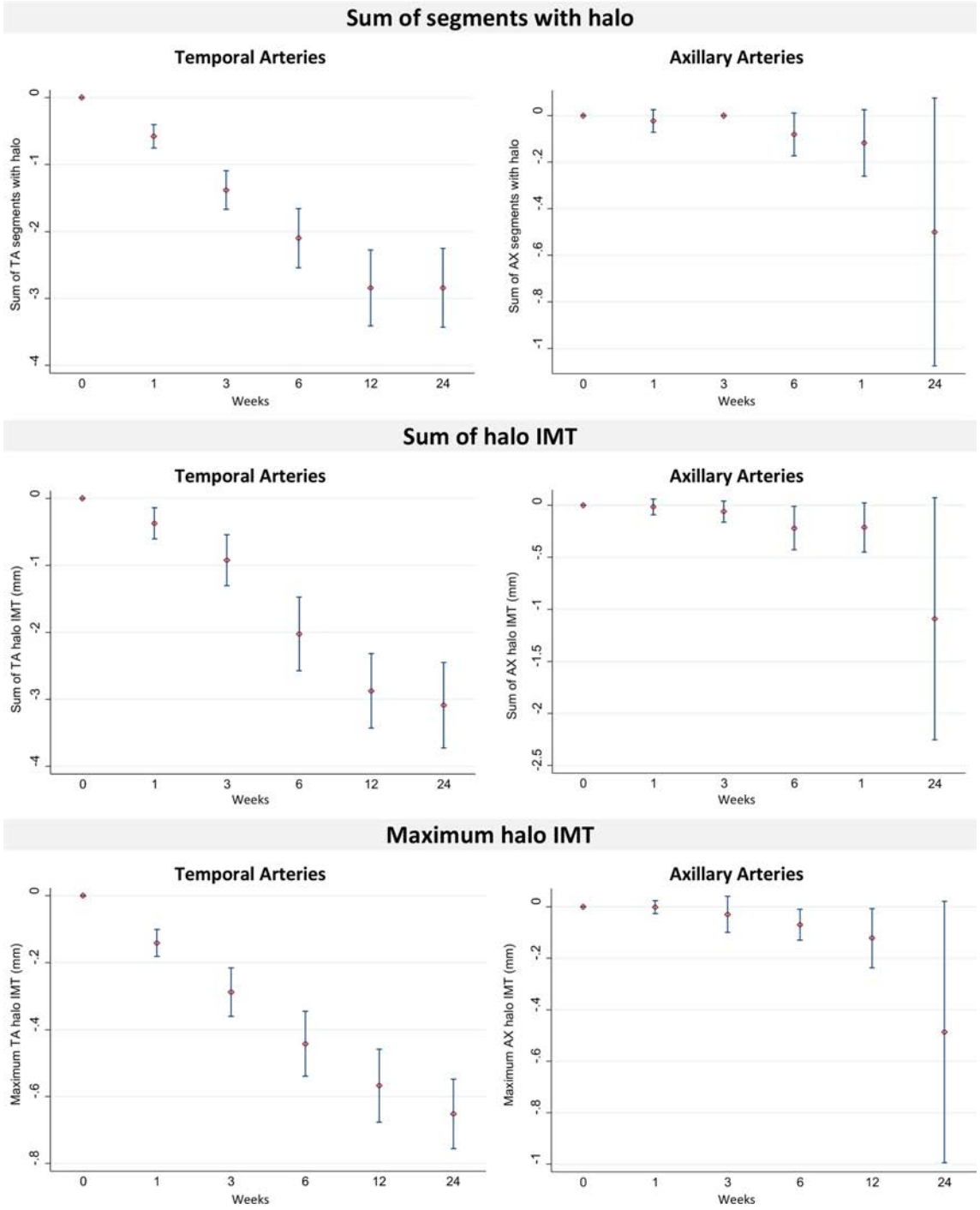


Figure 2 Mean variation (not standardised) of temporal and axillary halo features at different time points. Mean variation (not standardised) of each halo feature is shown with 95% CI. Error bars crossing zero line indicate that the variation is not statistically significant at that particular time point. AX, axillary artery; IMT, intima–media thickness; TA, temporal artery.

between TA halo characteristics and values of ESR, CRP and BVAS, highlighting the non-specific nature of the current disease activity markers used to assess GCA. The likelihood of achieving disease remission was lower in patients with a higher number of TA arterial segments with halo (OR 0.39, $p<0.05$) and increased values of sum and maximum TA halo IMT (OR 0.34, $p<0.05$). By contrast, we could only observe an improvement of the AX halo features after week 6, specifically for the sum of halo IMT and maximum halo IMT (SMD from baseline of −0.81 and −0.94, respectively). In addition, during these 6 months of follow-up, the AX halo features showed no significant correlation with disease activity measures nor any association with attaining clinical remission. Although our cohort only included 11 (22.4%) patients with axillary involvement, our results corroborate those from prior studies in which AX halos persisted for longer than TA halos, irrespective of clinical remission.[34 38 40 49 50] They also support our previous findings,[48] in which there was no variation of the AX halo IMT within the first 7 days of treatment with high doses of GCs, in contrast to the TA halo IMT.

At week 24, TA halo features showed significant correlation with the cumulative dose of GCs, but not with the number of days on high doses of GCs (≥30 mg of prednisolone or equivalent),

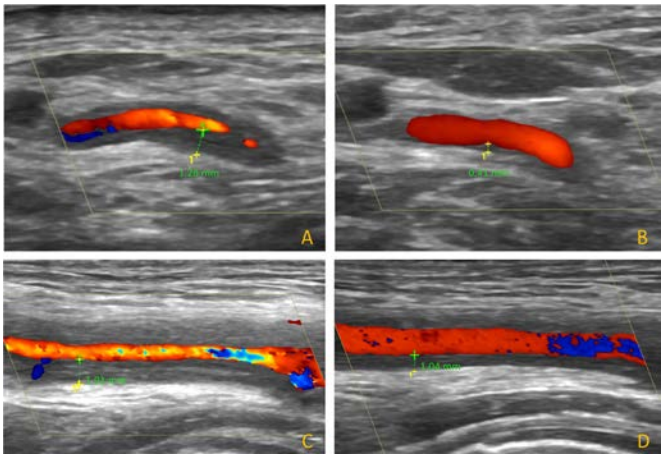


Figure 3 Ultrasound halo sign of the temporal and axillary arteries at baseline and week 24. Patient one (A and B); patient two (C and D). Both patients were in clinical and laboratory remission at week 24; however, patient two still presented an AX halo sign but with a lower IMT in comparison to baseline. (A) Left common superficial temporal artery at baseline showing a halo sign (maximum IMT of 1.28 mm). (B) Left common superficial temporal artery at week 24 with no halo sign (maximum IMT of 0.41 mm). (C) Left axillary artery at baseline showing a halo sign (maximum IMT of 1.91 mm). (D) Left axillary artery at week 24 still showing a halo sign (maximum IMT of 1.04 mm). IMT, intima–media thickness.

even when adjusted for DMARD concomitant treatment. This suggests that the cumulative effect of GCs may be more relevant than the actual time on high doses of GCs to reduce TA halo IMT and number of affected segments. In terms of AX halo features, no correlation was found with GC treatment. To the best of our knowledge, our study is the first to prospectively measure the direct consequences of GC treatment on halo features.

To confirm suspected relapse, EULAR guidelines recommended the use of imaging.[17] Our findings reinforce the utility of ultrasound in this setting, with 94% of first relapses showing the presence of halo sign, all with an increased IMT in comparison to the preceding ultrasonographic examination. Moreover, patients at first relapse had a lower number of arterial segments with halo and reduced size of TA halo IMT when compared with their disease presentation, which may potentially be missed by less experienced ultrasonographers. We have previously reported a lower proportion of patients with halo and fewer segments with vasculitic involvement in relapsing GCA, in comparison to patients with new-onset GCA.[29] However, in contrast to the present study, different patients were included in both groups, and all had more days of GC treatment.

This study has several strengths to highlight: (1) its prospective design; (2) ultrasound assessment performed according to a fixed protocol, therefore allowing for a standardised collection of data; (3) incorporation of various time points, including week 1 in which significant changes of TA halo features were verified; (4) high total number of prospective visits included (354 visits during the complete study period and 250 visits during the 6-month prospective assessment); (5) first-time evaluation of specific features of halo sign (number of segments with halo and halo IMT) at various time points for monitoring purposes; (6) assessment of both TA and AX halo features; (7) ultrasound evaluation performed by experienced ultrasonographers, who had undergone the same training, and using high-quality

Table 5 Correlation between halo features and glucocorticoid treatment

	Correlation coefficient	
	Number of days on GCs*	GC cumulative dose†
Number of arterial segments		
Sum of all segments with halo	−0.03	**−0.33**
Sum of TA segments with halo	−0.03	**−0.34**
Sum of AX segments with halo	−0.05	−0.07
Halo thickness		
Sum of all halo IMT (mm)	−0.05	**−0.34**
Sum of TA halo IMT (mm)	−0.05	**−0.37**
Sum of AX halo IMT (mm)	−0.06	−0.08
Maximum TA halo IMT (mm)	−0.07	**−0.32**
Maximum AX halo IMT (mm)	−0.05	−0.08

The magnitude of the correlation may be interpreted as follows: small (0.10–0.30), medium (0.30–0.50), large (0.50–0.70) and very large (0.70–1.00).
In bold the statistically significant results ($p<0.05$)
*≥30 mg/day of prednisolone or equivalent.
†Prednisolone or equivalent.
AX, axillary artery; GCs, glucocorticoids; IMT, intima–media thickness; TA, temporal artery.

Table 4 Association between halo features and disease activity markers

	Correlation coefficient			OR
	ESR*	CRP*	BVAS	Disease remission
Number of arterial segments				
Sum of all segments with halo	**0.44**	**0.36**	**0.29**	**0.47**
Sum of TA segments with halo	**0.41**	**0.34**	**0.29**	**0.39**
Sum of AX segments with halo	0.08	0.06	0.04	1.41
Halo thickness				
Sum of all halo IMT (mm)	**0.47**	**0.40**	**0.34**	**0.51**
Sum of TA halo IMT (mm)	**0.44**	**0.39**	**0.36**	**0.34**
Sum of AX halo IMT (mm)	0.09	0.07	0.06	1.41
Maximum TA halo IMT (mm)	**0.48**	**0.41**	**0.35**	**0.34**
Maximum AX halo IMT (mm)	0.08	0.07	0.04	1.38

The magnitude of the correlation may be interpreted as follows: small (0.10–0.30), medium (0.30–0.50), large (0.50–0.70) and very large (0.70–1.00). The higher the halo feature improvement, the higher the ESR/CRP/BVAS improvement.
*Increased values of ESR and CRP due to other reasons than vasculitis activity (eg, infections) were excluded from the analysis. In bold the statistically significant results ($p<0.05$).
AX, axillary artery; BVAS, Birmingham Vasculitis Activity Score; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IMT, intima–media thickness; TA, temporal artery.

Table 6 Comparison between halo features at disease presentation and disease relapse

	Disease presentation	Disease relapse*	P value†
Number of arterial segments			
Sum of all segments with halo; mean (SD) (n=16 patients)	4.85 (1.51)	2.93 (1.59)	**0.0012**
Sum of TA segments with halo; mean (SD) (n=14 patients)	4.71 (1.38)	2.48 (1.81)	**0.0012**
Sum of AX segments with halo; mean (SD) (n=3 patients)	2.00 (0.00)	1.33 (1.15)	0.3173
Halo thickness			
Sum of all halo IMT (mm); mean (SD) (n=16 patients)	4.49 (1.95)	2.01 (1.13)	**0.0012**
Sum of TA halo IMT (mm); mean (SD) (n=14 patients)	4.34 (1.82)	1.90 (1.25)	**0.0010**
Sum of AX halo IMT (mm); mean (SD) (n=3 patients)	3.03 (0.86)	2.45 (2.12)	0.5930
Maximum TA halo IMT (mm); mean (SD) (n=14 patients)	1.09 (0.35)	0.68 (0.25)	**0.0006**
Maximum AX halo IMT (mm); mean (SD) (n=3 patients)	1.64 (0.54)	1.34 (1.16)	0.5930

*For patients with more than one disease relapse, only the first one was included.
†Wilcoxon signed-rank test; In bold the statistically significant results (p<0.05).
AX, axillary artery; IMT, intima–media thickness; TA, temporal artery.

equipment;[29] and (8) all analyses performed on complete data, without imputation.

Nevertheless, this study has potential limitations to consider: (1) the ultrasonographers were not blinded to clinical data, although a standardised methodology was employed during the ultrasound assessment to reduce the risk of bias; (2) many of the patients included in this study were referred to us by the ophthalmology department, biasing our cohort towards a more cranial phenotype of the disease; (3) only 22% of cases presented with AX involvement at baseline, which may limit the interpretation of the vasculitic changes observed for this arterial segment; further prospective studies including more patients with AX involvement are warranted to confirm our findings; (4) a few patients were not able to attend all scheduled visits, although all time points had at least 80% of patients included; (5) 20/49 patients have received high doses of GCs before baseline, but their mean was only 2.5 days; (6) IMT prospective measurement was performed in the area with the greatest arterial wall thickness, which might not have captured the same level of change if a fixed location had been used; (7) in patients with a more chronic and less hypoechoic halo sign (eg, patients with a higher cumulative dose of GCs), distinction between the external layer of the IMT and the surrounding subcutaneous tissue may not be so evident as in those with a more acute halo sign; (8) differentiation between halo sign reflective of active disease or of wall scarring may be a challenge during follow-up and should be addressed in future research; and (9) the specificity of the changes in halo appearance over time should be correlated with clinical status in a larger cohort to address the value of these data in clinical practice.

In conclusion, ultrasound is a feasible imaging tool to monitor patients with GCA. Both TA and AX halo-specific features (number of segments with halo, sum of halo IMT and maximum halo IMT), in particular TA halo features, showed sensitivity to change during a 24-week follow-up period. In addition, a significant correlation was observed between TA halo features and disease activity markers and GC cumulative dose. The prognostic value of this sensitivity to change, in particular the different SMD magnitudes between time points for TA and AX halos, still needs to be addressed in future studies. Moreover, adequate training and expertise of the ultrasonographers performing the scans should always be ensured.[17 29] Nevertheless, our study suggests that a potential ultrasound composite score including halo size and extent, instead of the traditional binary presence/absence of halo sign, would be more suitable to assess disease activity and response to treatment in GCA. This could be particularly important for patients treated with IL-6 inhibitors, in whom CRP and ESR become unreliable to detect disease activity. Future clinical trials in GCA should evaluate direct treatment effect on halo features as an outcome measure of interest.

Author affiliations
[1]Rheumatology Department, Hospital de Santa Maria, Centro Hospitalar Universitario Lisboa Norte EPE, Lisboa, Portugal
[2]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal
[3]Rheumatology Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[4]PhD in Experimental Medicine, University of Pavia, Pavia, Italy
[5]Epidemiology Research Unit, Italian Society of Rheumatology, Milano, Italy
[6]Department of Medical Sciences, Rheumatology Unit, University of Ferrara, Ferrara, Italy
[7]Rheumatology Department, Centro Hospitalar Universitário do Algarve, Faro, Portugal
[8]Medical Centre for Rheumatology Berlin-Buch, Immanuel Krankenhaus Berlin, Berlin, Germany
[9]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

Correction notice This article has been corrected since it published Online First. The author affiliations have been amended.

Twitter Carlo Alberto Scirè @rthritis

Acknowledgements The authors would like to thank Dr. Andreas Diamantopoulos, Dr. Bhaskar Dasgupta and Dr. Ana Sofia Serafim for participating in the initial discussions regarding the construction of the PROTEA protocol.

Contributors All listed authors provided substantial contributions to this work. CP, SM, WS and RAL were involved in its conception and design. CP, SM, PD, NK, AM, VT, FB, FS, CM and JEF contributed to the acquisition of data. CAS conducted the statistical analyses. CP, SM, RAL and WS contributed to the interpretation of data. CP, SM, CAS and RAL drafted the manuscript. All authors contributed to the critical revision of the manuscript and agreed on its final version.

Funding CP's work was supported in part by a grant from the Portuguese Society of Rheumatology.

Competing interests None declared.

Patient and public involvement statement Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs
Cristina Ponte http://orcid.org/0000-0002-3989-1192
Sara Monti http://orcid.org/0000-0002-1800-6772
Carlo Alberto Scirè http://orcid.org/0000-0001-7451-0271
Paolo Delvino http://orcid.org/0000-0002-6383-8236
Vítor Teixeira http://orcid.org/0000-0002-9452-0028
Carlomaurizio Montecucco http://orcid.org/0000-0001-8263-3925
João Eurico Fonseca http://orcid.org/0000-0003-1432-3671

REFERENCES

1 Jennette JC, Falk RJ, Bacon PA. Revised international chapel Hill consensus conference Nomenclature of vasculitides. *Arthritis & Rheumatism* 2012;2013:1–11.
2 González-Gay MA, García-Porrúa C, Llorca J, *et al*. Visual manifestations of giant cell arteritis. trends and clinical spectrum in 161 patients. *Medicine* 2000;79:283–92.
3 Restuccia G, Boiardi L, Cavazza A, *et al*. Flares in biopsy-proven giant cell arteritis in northern Italy: characteristics and predictors in a long-term follow-up study. *Medicine* 2016;95:e3524.
4 Alba MA, García-Martínez A, Prieto-González S, *et al*. Relapses in patients with giant cell arteritis: prevalence, characteristics, and associated clinical findings in a longitudinally followed cohort of 106 patients. *Medicine* 2014;93:194–201.
5 Kermani TA, Warrington KJ, Cuthbertson D, *et al*. Disease relapses among patients with giant cell arteritis: a prospective, longitudinal cohort study. *J Rheumatol* 2015;42:1213–7.
6 Labarca C, Koster MJ, Crowson CS, *et al*. Predictors of relapse and treatment outcomes in biopsy-proven giant cell arteritis: a retrospective cohort study. *Rheumatology* 2016;55:347–56.
7 Martinez-Lado L, Calviño-Díaz C, Piñeiro A, *et al*. Relapses and recurrences in giant cell arteritis: a population-based study of patients with biopsy-proven disease from northwestern Spain. *Medicine* 2011;90:186–93.
8 Liozon E, Roblot P, Paire D, *et al*. Anticardiolipin antibody levels predict flares and relapses in patients with giant-cell (temporal) arteritis. A longitudinal study of 58 biopsy-proven cases. *Rheumatology* 2000;39:1089–94.
9 Proven A, Gabriel SE, Orces C, *et al*. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. *Arthritis Rheum* 2003;49:703–8.
10 Nesher G, Nesher R, Mates M, *et al*. Giant cell arteritis: intensity of the initial systemic inflammatory response and the course of the disease. *Clin Exp Rheumatol* 2008;26:S30–4.
11 Hernández-Rodríguez J, García-Martínez A, Casademont J, *et al*. A strong initial systemic inflammatory response is associated with higher corticosteroid requirements and longer duration of therapy in patients with giant-cell arteritis. *Arthritis Rheum* 2002;47:29–35.
12 Hachulla E, Boivin V, Pasturel-Michon U, *et al*. Prognostic factors and long-term evolution in a cohort of 133 patients with giant cell arteritis. *Clin Exp Rheumatol* 2001;19:171–6.
13 Graham E, Holland A, Avery A, *et al*. Prognosis in giant-cell arteritis. *Br Med J* 1981;282:269–71.
14 Monti S, Águeda AF, Luqmani RA, *et al*. Systematic literature review Informing the 2018 update of the EULAR recommendation for the management of large vessel vasculitis: focus on giant cell arteritis. *RMD Open* 2019;5:e001003.
15 Tse WY, Cockwell P, Savage CO. Assessment of disease activity in systemic vasculitis. *Postgrad Med J* 1998;74:1–6.
16 Stone JH, Tuckwell K, Dimonaco S, *et al*. Glucocorticoid dosages and Acute-Phase reactant levels at giant cell arteritis flare in a randomized trial of tocilizumab. *Arthritis & Rheumatology* 2019;71:1329–38.
17 Dejaco C, Ramiro S, Duftner C, *et al*. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis* 2018;77:636–43.
18 Arida A, Kyprianou M, Kanakis M, *et al*. The diagnostic value of ultrasonography-derived edema of the temporal artery wall in giant cell arteritis: a second meta-analysis. *BMC Musculoskelet Disord* 2010;11:44.
19 Karassa FB, Matsagas MI, Schmidt WA, *et al*. Meta-Analysis: test performance of ultrasonography for giant-cell arteritis. *Ann Intern Med* 2005;142:359.
20 Ball EL, Walsh SR, Tang TY, *et al*. Role of ultrasonography in the diagnosis of temporal arteritis. *Br J Surg* 2010;97:1765–71.
21 Duftner C, Dejaco C, Sepriano A, *et al*. Imaging in diagnosis, outcome prediction and monitoring of large vessel vasculitis: a systematic literature review and meta-analysis Informing the EULAR recommendations. *RMD Open* 2018;4:e000612.
22 Rinagel M, Chatelus E, Jousse-Joulin S, *et al*. Diagnostic performance of temporal artery ultrasound for the diagnosis of giant cell arteritis: a systematic review and meta-analysis of the literature. *Autoimmun Rev* 2019;18:56–61.
23 Hellmich B, Agueda A, Monti S, *et al*. 2018 update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis* 2020;79:19–30.
24 Hunder GG, Bloch DA, Michel BA, *et al*. The American College of rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis & Rheumatism* 2010;33:1122–8.
25 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.
26 Dasgupta B, Borg FA, Hassan N, *et al*. BSR and BHPR guidelines for the management of giant cell arteritis. *Rheumatology* 2010;49:1594–7.
27 Stone JH, Tuckwell K, Dimonaco S, *et al*. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med* 2017;377:317–28.
28 Monti S, Floris A, Ponte C, *et al*. The use of ultrasound to assess giant cell arteritis: review of the current evidence and practical guide for the rheumatologist. *Rheumatology* 2018;57:227–35.
29 Monti S, Floris A, Ponte CB, *et al*. The proposed role of ultrasound in the management of giant cell arteritis in routine clinical practice. *Rheumatology* 2018;57:112–9.
30 Terslev L, Hammer HB, Torp-Pedersen S, *et al*. EFSUMB minimum training requirements for rheumatologists performing musculoskeletal ultrasound. *Ultraschall Med* 2013;34:475–7.
31 Quinn KA, Ahlman MA, Malayeri AA, *et al*. Comparison of magnetic resonance angiography and ^{18}F-fluorodeoxyglucose positron emission tomography in large-vessel vasculitis. *Ann Rheum Dis* 2018;77:1165–71.
32 Reichenbach S, Adler S, Bonel H, *et al*. Magnetic resonance angiography in giant cell arteritis: results of a randomized controlled trial of tocilizumab in giant cell arteritis. *Rheumatology* 2018;57:982–6.
33 De Miguel E, Roxo A, Castillo C, *et al*. The utility and sensitivity of colour Doppler ultrasound in monitoring changes in giant cell arteritis. *Clin Exp Rheumatol* 2012;30:S34–8.
34 Aschwanden M, Schegk E, Imfeld S, *et al*. Vessel wall plasticity in large vessel giant cell arteritis: an ultrasound follow-up study. *Rheumatology* 2019;58:792–7.
35 Pérez López J, Solans Laqué R, Bosch Gil JA, *et al*. Colour-duplex ultrasonography of the temporal and ophthalmic arteries in the diagnosis and follow-up of giant cell arteritis. *Clin Exp Rheumatol* 2009;27:S77–82.
36 Evangelatos G, Fragoulis GE, Iliopoulos A. Temporal ultrasound for monitoring tocilizumab treatment in giant cell arteritis: seeing beyond serum markers? *Ann Rheum Dis* 2021;80:e184.
37 Habib HM, Essa AA, Hassan AA. Color duplex ultrasonography of temporal arteries: role in diagnosis and follow-up of suspected cases of temporal arteritis. *Clin Rheumatol* 2012;31:231–7.
38 Schmidt WA, Moll A, Seifert A, *et al*. Prognosis of large-vessel giant cell arteritis. *Rheumatology* 2008;47:1406–8.
39 Czihal M, Piller A, Schroettle A, *et al*. Outcome of giant cell arteritis of the arm arteries managed with medical treatment alone: cross-sectional follow-up study. *Rheumatology* 2013;52:282–6.
40 Aschwanden M, Kesten F, Stern M, *et al*. Vascular involvement in patients with giant cell arteritis determined by duplex sonography of 2x11 arterial regions. *Ann Rheum Dis* 2010;69:1356–9.
41 Czihal M, Schröttle A, Baustel K. B-Mode sonography wall thickness assessment of the temporal and axillary arteries for the diagnosis of giant cell arteritis: a cohort study. *Clin Exp Rheumatol* 2017;6 https://pubmed.ncbi.nlm.nih.gov/28375835/
42 Schäfer VS, Juche A, Ramiro S, *et al*. Ultrasound cut-off values for intima-media thickness of temporal, facial and axillary arteries in giant cell arteritis. *Rheumatology* 2017;56:1479–83.
43 Monti S, Ponte C, Pereira C. The impact of disease extent and severity detected by quantitative ultrasound analysis in the diagnosis and outcome of giant cell arteritis. *Rheumatology* 2019:kez554.
44 van der Geest KSM, Borg F, Kayani A, *et al*. Novel ultrasonographic halo score for giant cell arteritis: assessment of diagnostic accuracy and association with ocular ischaemia. *Ann Rheum Dis* 2020;79:393–9.
45 Ješe R, Rotar Žiga, Tomšič M, *et al*. The cut-off values for the intima-media complex thickness assessed by colour Doppler sonography in seven cranial and aortic arch arteries. *Rheumatology* 2021;60:1346-1352.
46 Hauenstein C, Reinhard M, Geiger J, *et al*. Effects of early corticosteroid treatment on magnetic resonance imaging and ultrasonography findings in giant cell arteritis. *Rheumatology* 2012;51:1999–2003.
47 Santoro L, D'Onofrio F, Bernardi S, *et al*. Temporal ultrasonography findings in temporal arteritis: early disappearance of halo sign after only 2 days of steroid treatment. *Rheumatology* 2013;52:622.
48 Ponte C, Serafim AS, Monti S, *et al*. Early variation of ultrasound halo sign with treatment and relation with clinical features in patients with giant cell arteritis. *Rheumatology* 2020;59:3717–26.
49 Czihal M, Piller A, Schroettle A, *et al*. Outcome of giant cell arteritis of the arm arteries managed with medical treatment alone: cross-sectional follow-up study. *Rheumatology* 2013;52:282–6.
50 Ford JA, Dilorio MA, Huang W, *et al*. Follow-Up vascular ultrasounds in patients with giant cell arteritis. *Clin Exp Rheumatol* 2020;38 Suppl 124:107–11.

EPIDEMIOLOGICAL SCIENCE

Serum uric acid control for prevention of gout flare in patients with asymptomatic hyperuricaemia: a retrospective cohort study of health insurance claims and medical check-up data in Japan

Ruriko Koto ,[1] Akihiro Nakajima,[2] Hideki Horiuchi,[1] Hisashi Yamanaka[3,4,5]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220439).

[1]Medical Science Department, Teijin Pharma Limited, Chiyoda-ku, Tokyo, Japan
[2]Pharmaceutical Development Administration Department, Teijin Pharma Limited, Chiyoda-ku, Tokyo, Japan
[3]Rheumatology, Sanno Medical Center, Tokyo, Japan
[4]Department of Rheumatology, International University of Health and Welfare, Chiba, Japan
[5]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

Correspondence to
Ruriko Koto, Medical Science Department, Teijin Pharma Limited, Chiyoda-ku, Tokyo 100-8585, Japan; r.koutou@teijin.co.jp

Portions of these data were presented in abstract form at the ACR Convergence 2020 (5–9 November 2020).

Received 26 March 2021
Accepted 5 June 2021
Published Online First 22 June 2021

To cite: Koto R, Nakajima A, Horiuchi H, *et al*. *Ann Rheum Dis* 2021;**80**:1483–1490.

ABSTRACT

Objectives In patients with gout, treating to target serum uric acid levels (sUA) of ≤6.0 mg/dL is universally recommended to prevent gout flare. However, there is no consensus on asymptomatic hyperuricaemia. Using Japanese health insurance claims data, we explored potential benefits of sUA control for preventing gout flare in subjects with asymptomatic hyperuricaemia.

Methods This retrospective cohort study analysed the JMDC Claims Database from April 2012 through June 2019. Subjects with sUA ≥8.0 mg/dL were identified, and disease status (prescriptions for urate-lowering therapy (ULT), occurrence of gout flare, sUA) was investigated for 1 year. Time to first onset and incidence rate of gout flare were determined by disease status subgroups for 2 years or more. The relationship between gout flare and sUA control was assessed using multivariable analysis.

Results The analysis population was 19 261 subjects who met eligibility criteria. We found fewer occurrences of gout flare, for both gout and asymptomatic hyperuricaemia, in patients who achieved sUA ≤6.0 mg/dL with ULT than in patients whose sUA remained >6.0 mg/dL or who were not receiving ULT. In particular, analysis by a Cox proportional-hazard model for time to first gout flare indicated that the HR was lowest, at 0.45 (95% CI 0.27 to 0.76), in subjects with asymptomatic hyperuricaemia on ULT (5.0<sUA ≤ 6.0 mg/dL), compared with untreated subjects (sUA ≥8.0 mg/dL).

Conclusions Occurrences of gout flare were reduced by controlling sUA at ≤6.0 mg/dL in subjects with asymptomatic hyperuricaemia as well as in those with gout.

Trial registration number UMIN000039985.

Key messages

What is already known about this subject?

► For adequate management of gout, guidelines around the world consistently recommend the use of urate-lowering therapy (ULT) to maintain serum uric acid levels (sUA) of ≤ 6.0 mg/dL.

What does this study add?

► In both patients population with asymptomatic hyperuricaemia and those with gout, our study indicates that the occurrence of gout flare can be lowered by using ULT to maintain sUA≤6.0 mg/dL.

How might this impact clinical practice or future developments?

► This study suggests that, in subjects with asymptomatic hyperuricaemia, control of sUA may provide long-term benefits by reducing or eliminating future occurrences of gout flare.

INTRODUCTION

In gout, hyperuricaemia causes abnormal urate deposition throughout the body.[1 2] The disease manifests as painful gout flares, which occur episodically in many patients with gout and constitute a significant clinical burden.[3] For adequate management of gout, guidelines around the world consistently recommend the use of urate-lowering therapy (ULT) in a treat-to-target approach to maintain serum uric acid levels (sUA) of ≤6.0 mg/dL.[1 2 4–6]

The risk of gout flare can be reduced by introducing ULT early in the clinical course of the disease,[7 8] and European and US guidelines now generally recommend initiation of ULT at the first gout flare under specific conditions.[4 5] However, there is no consensus on whether ULT should be prescribed prophylactically for patients with asymptomatic hyperuricaemia before the first gout flare. European and US guidelines do not recommend ULT for asymptomatic hyperuricaemia. This may be because there is insufficient accumulated data from patients with asymptomatic hyperuricaemia in those countries to provide appropriate guidance. In contrast, Japanese guidelines for gout and hyperuricaemia recommend the introduction of ULT under specific conditions to prevent gout flare in patients having asymptomatic hyperuricaemia with sUA of ≥8.0 mg/dL.[2 6] As a result, real-world treatment outcome data from patients with asymptomatic hyperuricaemia have been collected in Japan in the course of daily clinical practice. Previously, we found that most patients with gout or asymptomatic hyperuricaemia failed to meet their sUA targets in Japan.[9] Meanwhile, questions remain on whether ULT-induced reduction of sUA truly improves the patient's subsequent clinical course or reduces disease burden. In addition, although randomised controlled trials (RCTs) of patients with asymptomatic hyperuricaemia have shown that the ULT febuxostat suppresses gout flares compared with placebo[10] or control,[11 12] real-world evidence is not

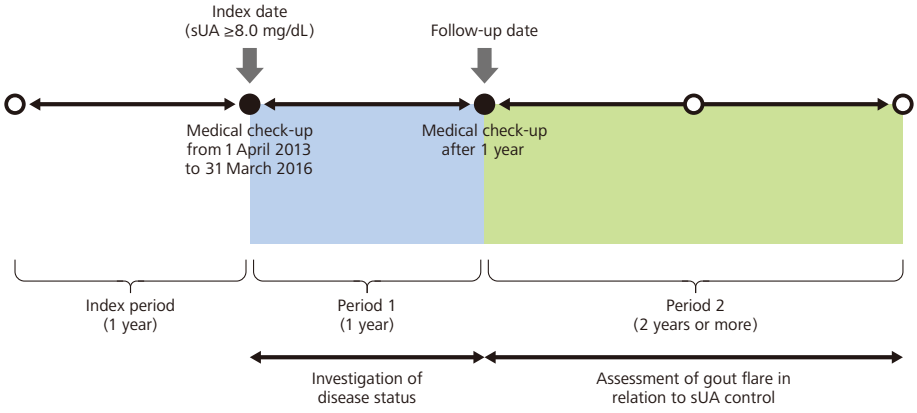


Figure 1 Study design. sUA, serum uric acid levels.

yet available on the relationship between gout flare and sUA in such patients.

We used data from health insurance claims and medical check-ups in a real-world setting to explore the research question, 'In patients with asymptomatic hyperuricaemia, is control of sUA (measured by whether or not sUA is maintained at ≤6.0 mg/dL or exceeds that amount) associated with subsequent risk of gout flare?'

METHODS

Study design and setting

This retrospective cohort study incorporated data from the JMDC Claims Database, including records of Japanese health insurance claims and medical check-ups from April 2012 through June 2019. JMDC collects information from multiple in-country organisations that provide health insurance coverage to Japanese employees and their dependents.[13] Data include diagnostic codes, drug prescriptions and information from annual medical check-ups for each person.

Subjects with sUA ≥8.0 mg/dL at one or more medical check-ups from 1 April 2013 to 31 March 2016 were identified. The study consisted of three distinct periods: the index period, period 1 and period 2. The index date was defined as the time of the earliest medical check-up showing sUA ≥8.0 mg/dL, and the month of that medical check-up was termed the index month. The index period was the year prior to (and excluding) the index date. Period 1 started on the index date and ended on the date of the subject's next annual medical check-up (follow-up date). Period 2 started on the day after the follow-up date (figure 1).

Participants

Subjects were included in the study if they had sUA≥8.0 mg/dL at one or more medical check-ups from 1 April 2013 to 31 March 2016, estimated glomerular filtration rate (eGFR) data available at the index date, and sUA data available 1 year after the index date, were at least 18 years of age on the index date, and were continuously registered in the JMDC Claims Database from 12 months before the index month to 24 months after the follow-up date.

To focus on patients who had asymptomatic hyperuricaemia (sUA ≥8.0 mg/dL) that was newly detected at a medical check-up after the index period, subjects were excluded from the study if at least once during the index period they were diagnosed with gout (ICD10 code M10) or asymptomatic hyperuricaemia (ICD10 code E790). Subjects were also excluded if they were prescribed ULT or if they were diagnosed with malignant tumours (ICD10 code C00-C97, D00-D09) during that period.

ULT was defined as any drug designated with ATC code M04 (antigout preparations), except for colchicine. Definitions of patient characteristics and drugs are presented in online supplemental table S1.

Study measures

During period 1, disease status was investigated for each individual subject, including the presence or absence of a ULT prescription, the presence or absence of gout flare and sUA at the follow-up date.

During period 2, the relationship between gout flare and sUA control was assessed, including time to first onset and incidence rate of gout flare. These data were calculated for each disease status subgroup as determined in period 1.

In this study, we used the term 'gout flare' when two parameters were satisfied. The first was a diagnosis of gout (ICD10 code M10) and prescriptions for antirheumatics, non-steroidal plain (ATC code M01A1) or oral corticosteroids, plain (ATC code H02A2) or colchicine (generic name), shown on the same insurance claim form. For the second, we confirmed the intervals between prescriptions for the above-mentioned drugs. We interpreted an interval of ≥14 days between the end of prescription for one drug and start of prescription for another drug as evidence of newly occurring gout flare. We used the term 'subject with gout' to indicate a subject who experienced gout flare, as defined above, during period 1, excluding subjects for whom treatment was not required (no prescription for ULT, and sUA <8.0 mg/dL at the follow-up date) under Japanese treatment guidelines.[2] Likewise, we used the term 'subject with asymptomatic hyperuricaemia' to indicate a subject who did not meet the definition of 'subject with gout' during period 1, excluding subjects for whom treatment was not required (no prescription for ULT, and sUA <8.0 mg/dL at the follow-up date).

Statistical methods

Our analysis included all subjects meeting the eligibility criteria. For period 1, an event tree was created using the presence or absence of a ULT prescription, the occurrence or non-occurrence of gout flare and sUA at the 1 year follow-up as the bifurcation

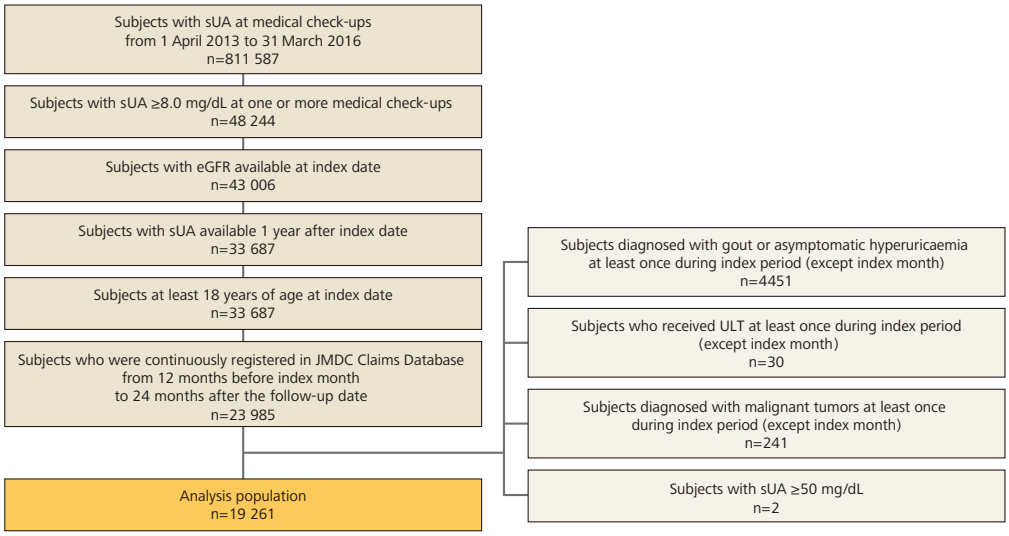


Figure 2 Subject disposition. eGFR, estimated glomerular filtration rate; sUA, serum uric acid levels; ULT, urate-lowering therapy.

points. Based on this event tree, subjects were classified into seven subgroups, including a group with sUA <8.0 mg/dL for whom treatment was not required.

The Kaplan-Meier method was used to estimate time to first gout flare in period 2 for each of the six disease status subgroups determined in period 1 (excluding subjects for whom no treatment was required). The median values and 95% CI were calculated. The time origin was the day after the follow-up date. For no events, the cut-off date was the first day of the month in which the subject terminated health insurance association membership. Univariable and multivariable analyses were performed using a Cox proportional-hazards model for subjects with asymptomatic hyperuricaemia and subjects with gout to calculate the HR. Explanatory variables were gender, age at follow-up date, eGFR at follow-up date, number of comorbidities and a combination of sUA range at follow-up date (sUA ≤5.0, 5.0<sUA ≤6.0, sUA ≤6.0, 6.0<sUA ≤7.0 and 7.0<sUA) and ULT usage (ULT (−) and ULT (+)) in period 1.

Among subjects with asymptomatic hyperuricaemia who were prescribed ULT during period 1, propensity score analyses compared the subject subgroups with sUA ≤6.0 mg/dL and sUA >6.0 mg/dL at the follow-up date. Details are provided in the online supplemental methods.

The incidence rate for gout flare during period 2 was calculated for each disease status subgroup as determined in period 1. Univariable and multivariable analyses, using a negative binomial regression model, were performed for each asymptomatic hyperuricaemia group and gout group to calculate the relative incidence rate. The explanatory variables were the same as used for Cox proportional-hazards model analysis. The log value of the follow-up period during period 2 was used as an offset variable.

All reported p values were two sided and were not adjusted for multiple testing. All analyses were performed using SAS V.9.4.

RESULTS

Study population

The population of 811 587 subjects had at least one sUA measurement at one or more medical check-ups from 1 April 2013 to 31 March 2016, with records showing that 48 244 of them had sUA≥8.0 mg/dL. Of those, 19 261 subjects met the inclusion criteria and did not meet the exclusion criteria (figure 2).

Subject characteristics

The overall study population (n=19 261) was predominantly man (98.3%), with a mean age ±SD of 43.2±9.4 years and mean sUA±SD of 8.47±0.53 mg/dL. The most frequent comorbidity was hypertension (13.5%), followed by hyperlipidaemia (11.5%) and renal dysfunction (eGFR <60 mL/min/1.73 m^2; 11.3%). A large portion of subjects (71.6%) had no comorbidities (table 1).

Disease status during period 1

We developed an event tree and summarised our study findings in 10 final nodes on that event tree. We then established seven subgroups of disease status, based on the findings shown in those 10 final nodes. The largest group of participants (n=10 480) showed sUA <8.0 mg/dL at their next check-up and were classified as 'no treatment required'. The next largest group consisted of patients who were not receiving ULT, had not experienced gout flare and continued to have sUA ≥8.0 mg/dL (n=7049). A total of 337 subjects with asymptomatic hyperuricaemia and 101 with gout had received ULT and reached sUA of ≤6.0 mg/dL by the follow-up date (figure 3).

Subject characteristics, organised by disease status, are shown in online supplemental table S2. In subjects with gout and those with asymptomatic hyperuricaemia, the subgroup of subjects on ULT with sUA ≤6.0 mg/dL tended to be older and to have more comorbidities, including hypertension and hyperlipidaemia, compared with the other subgroups. The subgroup on ULT with sUA >6.0 mg/dL had a higher percentage of subjects with renal dysfunction than the other subgroups.

Occurrence of gout flare in subjects with asymptomatic hyperuricaemia during period 2

In subjects with asymptomatic hyperuricaemia, the time to first gout flare was longest (median not reached) in the subgroup of subjects with sUA ≤6.0 mg/dL. The time to first gout flare was comparable between the subgroup with sUA >6.0 mg/dL and

Table 1 Subject characteristics

	Analysis population, n=19 261
Age, years	
Mean±SD	43.2±9.4
n (%)	
18–19	33 (0.2)
20–29	1572 (8.2)
30–39	4932 (25.6)
40–49	7593 (39.4)
50–59	4421 (23.0)
60–69	681 (3.5)
≥70	29 (0.2)
Sex, n (%)	
Male	18 924 (98.3)
Female	337 (1.7)
eGFR, mL/min/1.73 m^2*	
Mean±SD	75.59±14.15
n (%)	
≥90	2736 (14.2)
≥60,<90	14 339 (74.4)
≥30,<60	2150 (11.2)
≥15,<30	22 (0.1)
<15	14 (<0.1)
≥60	17 075 (88.7)
<60	2186 (11.3)
sUA, mg/dL	
Mean±SD	8.47±0.53
n (%)	
<8	0
≥8,<9	16 549 (85.9)
≥9,<10	2321 (12.1)
≥10	391 (2.0)
Comorbidities of interest, n (%)	
Hypertension	2591 (13.5)
Type 2 diabetes	983 (5.1)
Ischaemic heart disease	356 (1.8)
Heart failure	295 (1.5)
Cerebrovascular disease	271 (1.4)
Hyperlipidaemia	2212 (11.5)
Number of comorbidities, n (%)	
0	13 796 (71.6)
1	3380 (17.5)
2	1214 (6.3)
3	532 (2.8)
4	228 (1.2)
5	90 (0.5)
6	19 (<0.1)
7	2 (<0.1)
Concomitant medications, n (%)	
Antihyperlipidaemic drug	1315 (6.8)
ACE inhibitor	138 (0.7)
ARB	1712 (8.9)
Diuretic drug	385 (2.0)
Antidiabetic drug	407 (2.1)

*eGFR (male)=194 × $sCr^{-1.094}$ × $age^{-0.287}$, eGFR (female)=194 × $sCr^{-1.094}$ × $age^{-0.287}$ × 0.739.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; sUA, serum uric acid levels.

the untreated subgroup (median not reached for either group) (figure 4).

The incidence rate of gout flare was 0.033 (95% CI 0.023 to 0.043) flares/person-year for the subgroup of subjects with asymptomatic hyperuricaemia prescribed ULT and having sUA ≤6.0 mg/dL, 0.083 (95% CI 0.074 to 0.093) flares/person-year for the subgroup prescribed ULT and having sUA >6.0 mg/dL and 0.081 (95% CI 0.078 to 0.084) flares/person-year for those without ULT (figure 5).

From the results of Cox proportional-hazards model for time to first gout flare among the subjects on ULT, the HR was the lowest of 0.45 (95% CI 0.27 to 0.76) in subjects on ULT (5.0<sUA ≤ 6.0 mg/dL) compared with non-ULT subjects (sUA ≥8.0 mg/dL). From the results of a negative binomial regression model, the relative incidence rate was the lowest, at 0.40 (95% CI 0.24 to 0.68), in subjects on ULT (5.0<sUA ≤ 6.0 mg/dL) compared with non-ULT subjects (table 2). Findings were also recorded for multivariable and univariable analyses of time to first gout flare (online supplemental table S3) and the incidence rate for gout flare (online supplemental table S4).

Propensity score analyses were performed on subjects with asymptomatic hyperuricaemia who were receiving ULT. The C statistic was 0.689, and the p value for the Hosmer-Lemeshow test was 0.381. The intergroup distributions of baseline characteristics for the inverse probability weighting and propensity score-matched cohorts were better balanced than for the original cohort (online supplemental table S5).

Findings from the Kaplan-Meier curve and Cox proportional-hazard model are shown in online supplemental figure S1 and table S6). The HR for sUA ≤6.0 mg/dL compared with sUA >6.0 mg/dL for average treatment effect in the inverse probability of weighting (IPW) cohort was 0.48 (95% CI 0.30 to 0.79). Subjects who received ULT during period 1 and who showed sUA ≤6.0 mg/dL tended to have fewer attacks of gout flare than subjects with sUA >6.0 mg/dL. The results were robust because all analyses of our data provided similar findings (online supplemental table S6).

Occurrence of gout flare in subjects with gout during period 2

Among subjects with gout, the Kaplan-Meier curve for the group with sUA ≤6.0 mg/dL crossed the curves for both the group with sUA >6.0 mg/dL and the untreated subgroup (figure 4). The median time to first gout flare was 158.3 (95% CI 120.6 to –) in the untreated group and 156.6 (95% CI 113.3 to 198.7) in the sUA >6.0 mg/dL group. The median value was not reached in the sUA ≤6.0 mg/dL group.

The gout flare incidence rate was 0.333 (95% CI 0.275 to 0.391) flares/person-year for those on ULT with sUA ≤6.0 mg/dL, 0.468 (95% CI 0.429 to 0.508) flares/person-year for those on ULT with sUA >6.0 mg/dL, and 0.491 (95% CI 0.423 to 0.560) flares/person-year for those who were not receiving ULT (figure 5). Based on results from a Cox proportional-hazards model, the HR was the lowest, at 0.65 (95% CI 0.40 to 1.05), in subjects on ULT (5.0<sUA ≤ 6.0 mg/dL) compared with non-ULT subjects (sUA ≥8.0 mg/dL). A negative binomial regression indicated that the relative incidence rate was the lowest, at 0.54 (95% CI 0.33 to 0.91), in subjects on ULT (5.0<sUA ≤ 6.0 mg/dL) compared with non-ULT subjects (table 2).

DISCUSSION

In this study, we hypothesised that gout flare would be less common in patients whose sUA was decreased by ULT than in patients whose sUA remained elevated, not only in subjects with gout, but also in those with asymptomatic hyperuricaemia. Because Japanese guidelines recommend the use of ULT in certain patients with asymptomatic hyperuricaemia, data were available to support our hypothesis.

Multivariable analysis consistently suggested that the risk of gout flare was lowest when sUA was reduced to 5.0 mg/

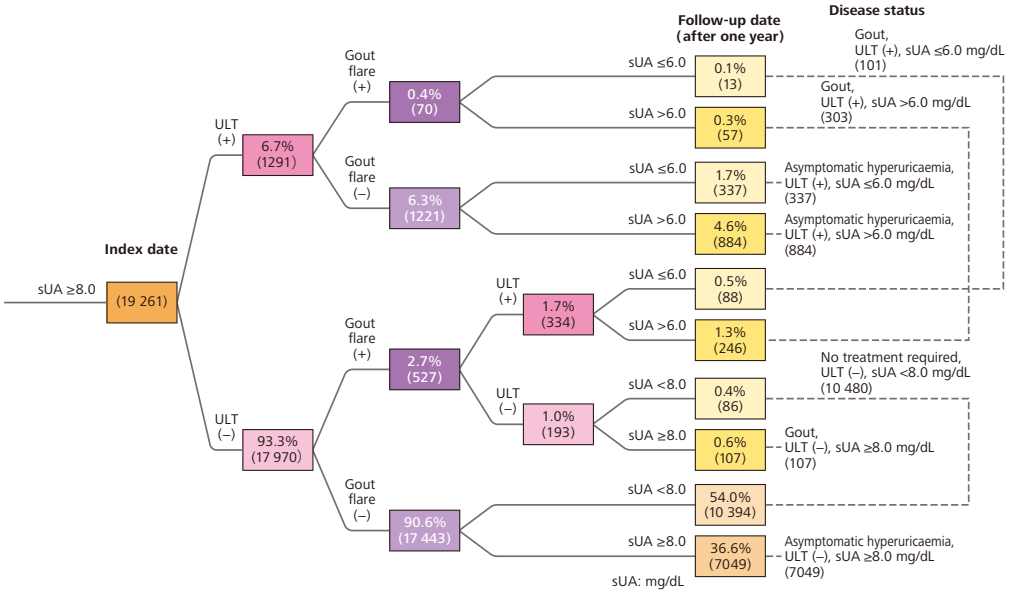
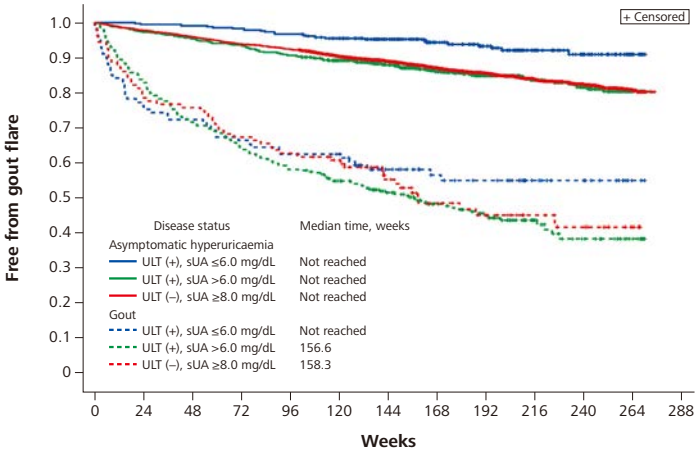


Figure 3 Event tree analysis of disease status from index date to follow-up date (period 1). Parentheses indicate the number of subjects. For percentages, the denominator was 19 261 subjects. sUA, serum uric acid levels; ULT, urate-lowering therapy.

dL<sUA ≤6.0 mg/dL, both for asymptomatic hyperuricaemia and for gout. However, when we analysed time to first gout flare, we found that subjects with gout whose sUA was reduced to ≤5.0 mg/dL were at higher risk for gout flare. Based on the finding that the Kaplan-Meier curve for the sUA ≤6.0 mg/dL group crossed the curves for the sUA >6.0 mg/dL group and the untreated group, we deduced that excessively rapid reduction of sUA may induce gout flare in the early phase of ULT introduction. This agrees with results from multiple previous studies, which showed that a sharp reduction in sUA during the initial phase of ULT was associated with gout flare.[14 15] Interestingly, our study showed this relationship only for gout, not for asymptomatic



Disease status		Weeks												
		0	24	48	72	96	120	144	168	192	216	240	264	288
Asymptomatic hyperuricaemia	ULT (+), sUA ≤6.0 mg/dL	337	335	334	331	326	312	266	191	160	96	67	22	0
	ULT (+), sUA >6.0 mg/dL	884	860	843	826	801	751	661	492	404	243	171	35	0
	ULT (–), sUA ≥8.0 mg/dL	7049	6893	6758	6617	6512	6137	5119	3872	3197	1794	1287	363	0
Gout	ULT (+), sUA ≤6.0 mg/dL	101	77	73	67	63	62	44	35	31	19	13	2	0
	ULT (+), sUA >6.0 mg/dL	303	252	217	195	176	156	124	92	72	39	25	10	0
	ULT (–), sUA ≥8.0 mg/dL	107	85	81	72	67	61	46	31	24	16	12	5	0

Figure 4 Kaplan-Meier curve for time to first gout flare in period 2. sUA, serum uric acid levels; ULT, urate-lowering therapy.

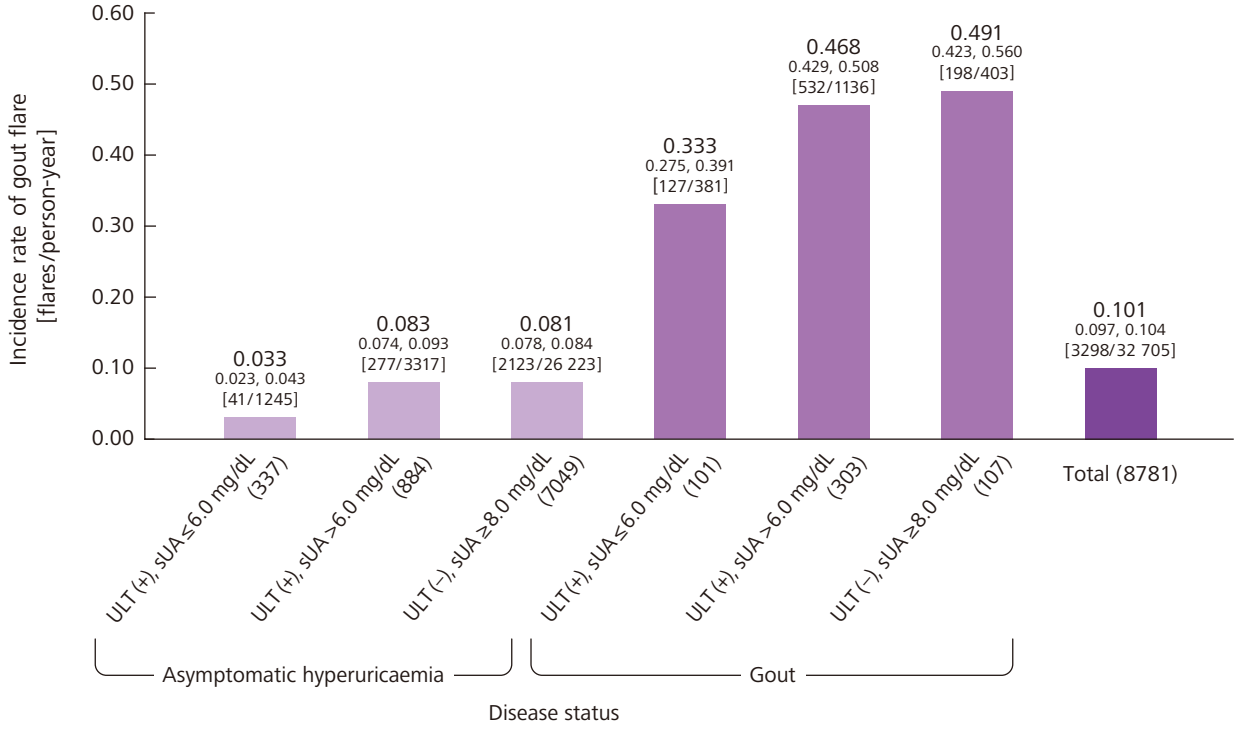


Figure 5 Incidence rate of gout flare during period 2. Numbers on top indicate the incidence rate, and numbers below them indicate the 95% CI. Brackets indicate the number of flares/person-year. Parentheses indicate the number of subjects. sUA, serum uric acid levels; ULT, urate-lowering therapy.

hyperuricaemia, possibly because of differences between the two groups in the amount of urate deposited in body tissues.

Propensity score analyses were applied to subjects with asymptomatic hyperuricaemia who were prescribed ULT, to compare findings between the group that reached the target sUA for patients with gout (sUA ≤6.0 mg/dL) and the group that did not. IPW analysis and propensity score matching analysis yielded consistent results, with lower levels of gout flare in subjects whose sUA was reduced by ULT to the gout target level. These results were robust and did not contradict the findings from our previous retrospective observational study, which also used the JMDC database and showed that subjects experienced less gout flare when they practiced closer adherence to ULT and when their sUA was monitored regularly.[16]

In patients with gout, the treat-to-target approach is widely accepted.[1 4] There is currently no consensus on whether sUA should be lowered to the gout target level in patients with asymptomatic hyperuricaemia since limited evidence is available to support this treatment option. However, in a recent randomised controlled study of asymptomatic hyperuricaemia in chronic kidney disease (CKD), researchers confirmed that the incidence proportion of gout flare was significantly lower (0.91% vs 5.86%) in patients treated with ULT than in those treated with a placebo.[10] Our study supports those findings, showing that the incidence rate of gout flare was lowered by using ULT to maintain sUA at the gout target level in subjects with asymptomatic hyperuricaemia as well as in those with gout. However, in patients with asymptomatic hyperuricaemia the incidence of gout over a 3 year period was 4.8% in subjects in the ULT group who reached sUA≤6.0 mg/dL and 11.1% in the untreated group. In other words, the number needed to treat (NNT) for 3 years to prevent 1 incident of gout flare was 16 patients. Similarly, previous RCTs in patients with asymptomatic hyperuricaemia indicated the NNT for 3 years to prevent a single gout flare was 24 patients.[4 10 17] In addition, results from two recent randomised clinical trials showed that, among those with asymptomatic hyperuricaemia and CKD, allopurinol provided no renoprotective benefits and potentially doubled the risk of death.[18–20] Clearly, the introduction of ULT for asymptomatic hyperuricaemia should be considered only after carefully assessing the clinical risks and benefits and the health economics of such treatment.

This study was significantly strengthened by using a large-scale medical information database that allowed us to follow approximately 20 000 subjects with asymptomatic hyperuricaemia for at least 2 years. Our study was feasible because Japan is one of the few countries where asymptomatic hyperuricaemia is treated, and records of that treatment are available. It would be much more challenging to observe asymptomatic hyperuricaemia treatment results in most other countries.

There are several limitations to this study. First, no validation study was conducted on the definitions of disease and outcome, so the applicability of those definitions is limited. Second, the JMDC database contains information from health insurance associations that include only limited data from subjects aged 65 and older and no data from those aged 75 and older, so our findings cannot be generalised to the entire Japanese population. Third, the study was limited to annual medical check-up data, so sUA were measured only once a year in most cases, and subjects might not have taken their ULT or other drugs on the day of the check-up. Fourth, there was a possibility of selection bias because the study was limited to subjects for whom sUA were available from medical check-ups for at least two consecutive years and who could be followed up for an additional 2 years. Fifth, to answer the research question, it was necessary to set the time origin for evaluation of gout flare during period 2 as the day after the next measurement of sUA (the follow-up date). This resulted in different dates for gout flare onset and

Table 2 Covariate-adjusted analysis for time to first onset and incidence rate of gout flare in period 2

	ULT (–)	ULT (+)			
	sUA, mg/mL	sUA, mg/mL			
	≥8.0	≤5.0	>5.0, ≤6.0	>6.0, ≤7.0	>7.0
Asymptomatic hyperuricaemia					
	n=7049	n=88	n=249	n=358	n=526
Time to first gout flare in period 2					
Median time (95% CI)	–	–	–	–	–
HR (95% CI) versus ULT (–)*	–	0.64 (0.32 to 1.29)	0.45 (0.27 to 0.76)	0.97 (0.71 to 1.32)	1.29 (1.04 to 1.61)
P value versus ULT (–)*	–	0.216	0.002	0.839	0.022
Incidence rate of gout flare in period 2					
Incidence rate (95% CI)†, flares/person-year	0.035 (0.024 to 0.051)	0.023 (0.010 to 0.053)	0.014 (0.008 to 0.027)	0.032 (0.019 to 0.053)	0.043 (0.027 to 0.068)
RR (95% CI) versus ULT (–)†	–	0.65 (0.31 to 1.39)	0.40 (0.24 to 0.68)	0.91 (0.64 to 1.31)	1.23 (0.93 to 1.63)
P value versus ULT (–)†	–	0.269	0.001	0.624	0.141
Gout					
	n=107	n=33	n=68	n=102	n=201
Time to first gout flare in period 2					
Median time (95% CI)	158.3 (120.6 to –)	127.6 (14.9 to –)	– (164.6 to –)	– (176.3 to –)	125.6 (87.3 to 157.1)
HR (95% CI) versus ULT (–)*	–	1.22 (0.71 to 2.10)	0.65 (0.40 to 1.05)	0.76 (0.51 to 1.14)	1.23 (0.89 to 1.70)
P value versus ULT (–)*	–	0.465	0.078	0.179	0.207
Incidence rate of gout flare in period 2					
Incidence rate (95% CI)†, flares/person-year	0.298 (0.096 to 0.924)	0.263 (0.077 to 0.894)	0.162 (0.051 to 0.516)	0.273 (0.091 to 0.823)	0.286 (0.094 to 0.869)
RR (95% CI) versus ULT (–)†	–	0.88 (0.48 to 1.63)	0.54 (0.33 to 0.91)	0.92 (0.59 to 1.42)	0.96 (0.66 to 1.39)
P value versus ULT (–)†	–	0.690	0.020	0.694	0.822

*Multivariable analysis using Cox proportional-hazards model. Sex, number of comorbidities of interest in period 1, and age, eGFR, and sUA control at the follow-up date were included in the model.
†Multivariable analysis using negative binomial regression model. Sex, number of comorbidities of interest in period 1, and age, eGFR, and sUA control at the follow-up date were included in the model.
RR, relative incidence rate; sUA, serum uric acid levels; ULT, urate-lowering therapy.

uric acid measurement, and meant that variable risk levels were represented within the patient group with gout. The nature of this study placed limitations on our ability to adjust for these confounding factors. Finally, although multivariable analysis and propensity score analyses were adjusted for confounding factors, the study may have been limited by unrecognised or unmeasured confounding factors.

Our study used real-world data to demonstrate that the occurrence of gout flare in asymptomatic hyperuricaemia and gout tended to be lower for patients who were prescribed ULT and achieved sUA ≤6.0 mg/dL than for those who received ULT treatment but whose sUA remained >6.0 mg/dL and for those who were untreated. Further exploration is warranted regarding the benefits and drawbacks of introducing ULT as a treatment for asymptomatic hyperuricaemia, both clinically and from the perspective of health economics.

Correction notice This article has been corrected since it published Online First. The dupilcate supplemental file has been removed.

Acknowledgements Review of the statistical analysis plan, clinical study report and manuscript was provided by Hirotaka Mano, Pharmaceutical Development Administration Department, Teijin Pharma Limited. Medical writing support was provided by EDIT, Inc. (Tokyo, Japan) and was funded by Teijin Pharma Limited.

Contributors RK drafted the manuscript, and AN performed the statistical analysis. All authors participated in the design of study and the analysis and/or interpretation of data. All authors have read and approved this final version of the manuscript for submission.

Funding This study was supported by Teijin Pharma Limited.

Competing interests RK, AN and HH are employees of Teijin Pharma Limited, and HY reports grants and personal fees from Teijin Pharma Limited.

Patient consent for publication Not required.

Ethics approval Since these data were thoroughly anonymised, ethics approval was not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iD
Ruriko Koto http://orcid.org/0000-0001-9201-1273

REFERENCES

1 Kiltz U, Smolen J, Bardin T, *et al*. Treat-to-target (T2T) recommendations for gout. *Ann Rheum Dis* 2017;76:632–8.
2 Yamanaka H, The guideline revising committee of the Japanese Society of Gout and Nucleic Acid Metabolism. Essence of the revised guideline for the management of hyperuricemia and gout. *Japan Med Assoc J* 2012;55:324–9.
3 Jackson R, Shiozawa A, Buysman EK, *et al*. Flare frequency, healthcare resource utilization and costs among patients with gout in a managed care setting: a retrospective medical claims-based analysis. *BMJ Open* 2015;5:e007214.
4 FitzGerald JD, Dalbeth N, Mikuls T, *et al*. 2020 American College of Rheumatology guideline for the management of gout. *Arthritis Care Res* 2020;72:744–60.
5 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.
6 Hisatome I, Ichida K, Mineo I, *et al*. Japanese Society of gout and nucleic acids 2019 guidelines for management of hyperuricemia and gout 3 edition. *Gout and Uric and Nucleic Acids* 2020;44 supple:1–40.
7 Rothenbacher D, Primatesta P, Ferreira A, *et al*. Frequency and risk factors of gout flares in a large population-based cohort of incident gout. *Rheumatology* 2011;50:973–81.
8 Dalbeth N, Saag KG, Palmer WE, *et al*. Effects of febuxostat in early gout: a randomized, double-blind, placebo-controlled study. *Arthritis Rheumatol* 2017;69:2386–95.
9 Koto R, Nakajima A, Horiuchi H, *et al*. Real-world treatment of gout and asymptomatic hyperuricemia: a cross-sectional study of Japanese health insurance claims data. *Mod Rheumatol* 2021;31:261–9.
10 Kimura K, Hosoya T, Uchida S, *et al*. Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: a randomized trial. *Am J Kidney Dis* 2018;72:798–810.
11 Kojima S, Matsui K, Hiramitsu S, *et al*. Febuxostat for cerebral and cardiorenovascular events prevention study. *Eur Heart J* 2019;40:1778–86.
12 Tanaka A, Taguchi I, Teragawa H, *et al*. Febuxostat does not delay progression of carotid atherosclerosis in patients with asymptomatic hyperuricemia: a randomized, controlled trial. *PLoS Med* 2020;17:e1003095.
13 Kimura S, Sato T, Ikeda S, *et al*. Development of a database of health insurance claims: standardization of disease classifications and anonymous record linkage. *J Epidemiol* 2010;20:413–9.
14 Yamanaka H, Tamaki S, Ide Y, *et al*. 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. *Ann Rheum Dis* 2018;77:270–6.
15 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.
16 Koto R, Nakajima A, Horiuchi H, *et al*. Factors associated with achieving target serum uric acid level and occurrence of gouty arthritis: a retrospective observational study of Japanese health insurance claims data. *Pharmacoepidemiol Drug Saf* 2021;30:157–68.
17 Liu P, Wang H, Zhang F, *et al*. The effects of allopurinol on the carotid intima-media thickness in patients with type 2 diabetes and asymptomatic hyperuricemia: a three-year randomized parallel-controlled study. *Intern Med* 2015;54:2129–37.
18 Gonzalez-Martin G, Cano J, Carriazo S, *et al*. The dirty little secret of urate-lowering therapy: useless to stop chronic kidney disease progression and may increase mortality. *Clin Kidney J* 2020;13:936–47.
19 Badve SV, Pascoe EM, Tiku A, *et al*. Effects of allopurinol on the progression of chronic kidney disease. *N Engl J Med* 2020;382:2504–13.
20 Doria A, Galecki AT, Spino C, *et al*. Serum urate lowering with allopurinol and kidney function in type 1 diabetes. *N Engl J Med* 2020;382:2493–503.

Elderly patients with comorbidities in the definition of difficult-to-treat rheumatoid arthritis

The advent of biological and targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) has improved the management of rheumatoid arthritis (RA) dramatically. However, there are patients who have not been controlled adequately, and EULAR has recently proposed a definition of difficult-to-treat RA (D2T RA).[1] We have verified the definition in our institution, where approximately 60% of 1700 patients with RA have been treated with b/tsDMARDs based on the EULAR recommendation and treat-to-target strategy,[2 3] resulting in roughly 85% achieving target (60% in remission and 25% in low disease activity),[4 5] and revealed that 10% are classified as D2T RA at the last visit.[5] In the process of this investigation, we further identified 77 patients (5%) who were on the borderline of non-D2T RA despite being in moderate or high disease activity due to non-fulfilment of the criterion of failure of two b/tsDMARDs with different mechanisms of action.[5]

We compared the characteristics of the 77 non-D2T RA patients in moderate or high disease activity with those of the non-D2T RA patients in remission or low disease activity (table 1). The patients in moderate or high disease activity were significantly older at diagnosis (62.3 vs 51.7 years, p<0.001) and latest visit (77.5 vs 62.9 years, p<0.001), had a longer disease duration (15.2 vs 11.3 years, p<0.001), more joint damage (Steinbrocker stage 4; 44.2 vs 23.8%, p<0.001) and significantly higher rheumatic disease comorbidity index[6] (2.2 vs 0.7, p<0.001). The

Table 1 Comparison of clinical characteristics between non-D2T RA in remission/LDA and MDA/HDA

	Non-D2T RA N=1536	Remission/LDA N=1459	MDA/HDA N=77	P value
Demographics				
Female	1268 (82.6)	1201 (82.3)	67 (87.0)	0.36
Age at diagnosis, years	52.1±15.5	51.6±15.4	62.3±14.0	<0.001
Age at last visit, years	63.4±1.7	62.9±14.6	77.5±10.4	<0.001
Disease duration, years	11.5±8.5	11.3±8.3	15.2±10.4	<0.001
BMI, n=1387	21.7±3.3	21.7±3.3	20.9±3.0	0.06
Disease characteristics				
DAS28-ESR	2.2±0.8	2.1±0.7	3.8±0.6	<0.001
CDAI	2.2±2.6	1.9±2.1	7.2±4.5	<0.001
SDAI	2.3±2.7	2.0±2.1	8.1±5.0	<0.001
TJC (0–28)	0.2±0.7	0.2±0.5	1.2±1.8	<0.001
SJC (0–28)	0.3±0.8	0.2±0.7	1.2±1.9	<0.001
EGA, mm	3.0±5.4	2.6±4.4	10.3±11.9	<0.001
PGA, mm	13.6±17.4	12.3±15.9	38.3±25.1	<0.001
HAQ-DI	0.4±0.3	0.4±0.6	1.2±0.9	<0.001
CRP, mg/dL	0.2±0.4	0.1±0.3	0.9±1.4	<0.001
ESR, mm/h	19.1±17.1	17.1±13.8	56.0±28.6	<0.001
MMP-3, mg/dL	57.3±61.8	53.3±49.8	136.5±153.8	<0.001
Anti-CCP positive	1112/1512 (73.5)	1052/1438 (73.2)	60/74 (81.2)	0.14
RF positive	1170 (76.2)	1101 (75.5)	69 (89.6)	0.004
Steinbrocker stage 4	381 (24.8)	347 (23.8)	34 (44.2)	<0.001
Current treatment				
csDMARDs alone	578 (37.6)	532 (36.5)	46 (59.7)	<0.001
MTX	956 (62.2)	923 (63.3)	33 (42.9)	<0.001
PSL use	161 (10.5)	140 (9.6)	21 (27.3)	<0.001
Dose of PSL, mg/day	3.6±1.9	3.6±1.9	4.1±2.1	0.21
b/tsDMARDs	854 (55.6)	827 (56.7)	27 (35.1)	<0.001
Treatment history				
Number of used csDMARDs	1.8±1.1	1.7±1.1	2.6±1.4	<0.001
Number of used b/tsDMARDs	1.0±1.1	1.0±1.1	0.6±0.7	<0.001
TNFi	692 (45.1)	676 (46.3)	16 (20.8)	<0.001
IL-6i	433 (28.2)	428 (29.3)	5 (6.5)	<0.001
CTLA-4Ig	160 (10.4)	143 (9.8)	17 (22.1)	0.002
tsDMARDs	28 (1.8)	28 (1.9)	0 (0)	<0.001
Contraindication or intolerance to MTX	241 (15.7)	209 (14.3)	32 (41.6)	<0.001
Admission history due to infection	75 (4.9)	52 (3.6)	23 (29.9)	<0.001

anti-CCP, anti-cyclic citrullinated peptide antibody; bDMARD, biologic disease-modifying anti-rheumatic drug; BMI, body mass index; CDAI, clinical disease activity index; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; CTLA-4Ig, cytotoxic T lymphocyte antigen-4Ig; DAS28, disease activity score for 28 joints; D2T RA, difficult-to-treat rheumatoid arthritis; EGA, evaluator global assessment; ESR, erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire- disability index; HDA, high disease activity; IL-6i, interleukin-6 receptor inhibitor; LDA, low disease activity; MDA, moderate disease activity; MMP-3, matrix metalloprotease-3; MTX, methotrexate; PGA, patient global assessment; PSL, prednisolone; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, simplified disease activity index; SJC, swollen joint count; TJC, tender joint count; TNFi, tumour necrosis factor inhibitor; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug.;

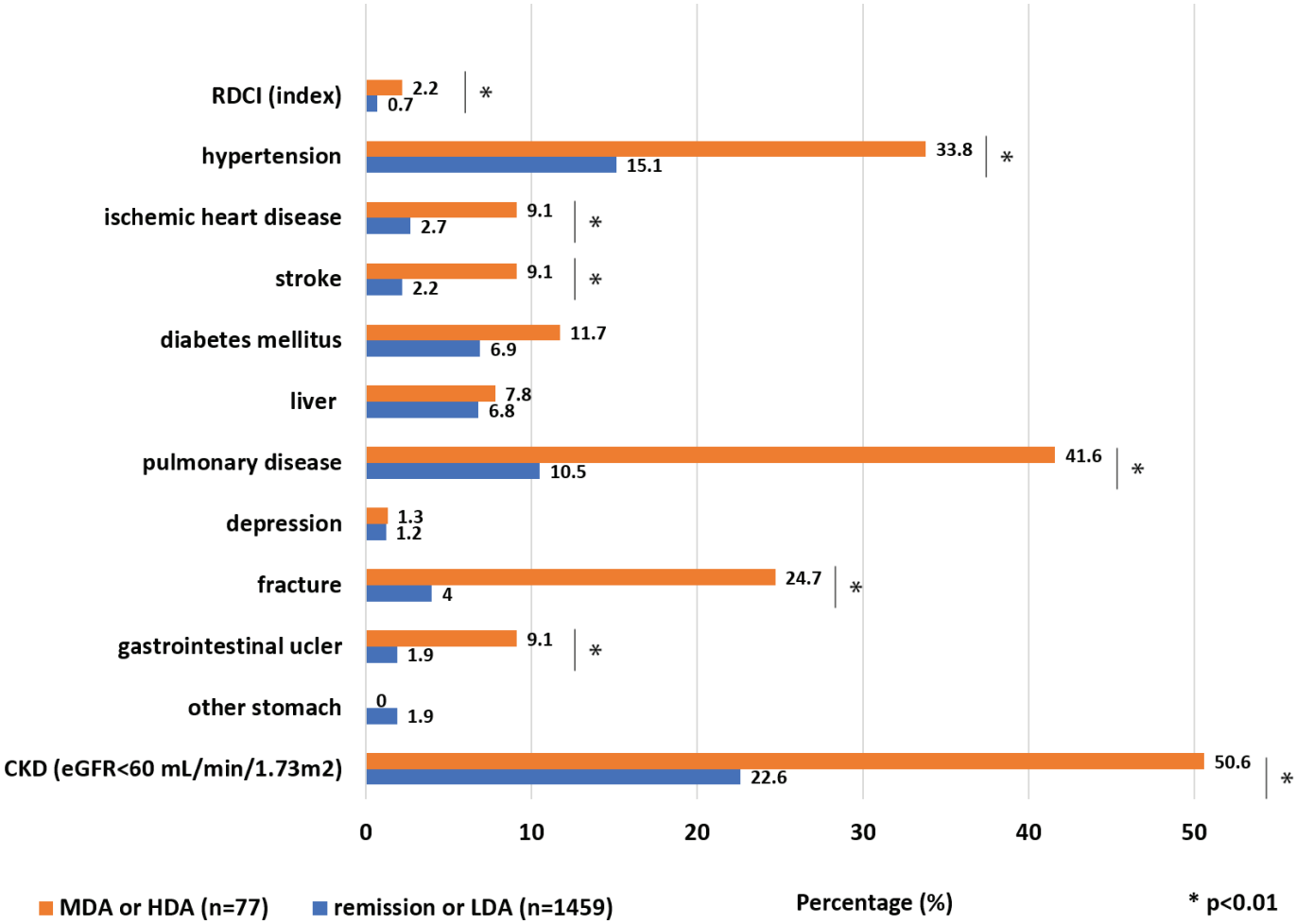


Figure 1 Comorbidities in patients with non-D2T RA in remission/LDA and in MDA/HDA. The patients in MDA/HDA were significantly higher rheumatic disease comorbidity index (p<0.001) and the frequent comorbidities were hypertension (p<0.001), ischaemic heart disease (p=0.008), stroke (p=0.003), pulmonary disease (p<0.001), chronic kidney disease (p<0.001) and fracture (p<0.001). CKD, chronic kidney disease; D2T RA, difficult-to-treat rheumatoid arthritis; eGFR, estimated glomerular filtration rate; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; RDCI, rheumatic disease comorbidity index.

frequent comorbidities were hypertension, ischaemic heart disease, stroke, pulmonary disease including interstitial lung disease and chronic pulmonary infection, chronic kidney disease and fracture (figure 1). Also, admission history due to infection (29.9% vs 3.6%, p<0.001) was significantly more frequent in the patients in moderate or high disease activity (table 1). The current use of methotrexate (42.9% vs 63.3%, p<0.001), b/tsDMARDs (35.1% vs 56.7%, p<0.001) and prednisolone (27.3 vs 9.6%, p<0.001) was also different between the two groups. These clinical characteristics are quite similar to those of patients with D2T RA patients due to comorbidity.[5] In the non-D2T RA patients in moderate or high disease activity treated with b/tsDMARDs, those drugs had been continued (not switched) for 5.6 years despite not achieving remission or low disease activity. In the patients who had previously treated with one b/tsDMARDs, another b/tsDMARDs had not been tried for 6.3 years at the latest visit. Those results suggest that T2T strategy and the current EULAR recommendations are difficult to implement for those frail patients with comorbidities because they or their attending physicians are reluctant to intensify or change treatment. If b/tsDMARDs are apparently contraindicated, those patients may be classified as D2T RA according to EULAR D2T RA definition,[1] however, assessing risk–benefit balance to adjust treatment in real world is not easy.

Along with longevity,[7] proportion of elderly patients and patients with later disease onset has been increasing in RA.[8] Elderly patients tend to have comorbidities and frailty, which could hamper intensive treatment including bDMARDs and/or tsDMARDs. The patients in our present study are representative for that portrait; they have not used ≥2 b/tsDMARDs with different mechanisms of action because they or their attending physicians did not decide to start b/tsDMARDs due to comorbidities or severe infection history, although those were not apparent contraindication. However, such patients are problematic because joint inflammation, laboratory findings including acute phase reactants and matrix metalloproteinase-3 and patient-reported outcomes are not well-controlled even after taking into consideration some non-inflammatory factors such as progressed joint damage associated with long disease duration (table 1). We need to recognise that D2T RA and even some non-D2T RA represent a heterogeneous patient population and seek for appropriate solution according to each status.

Our study can have some bias due to the nature of a single-centred study in Japan. The results should be validated with larger, worldwide studies in future. Since the publication of definition of D2T RA, several papers about D2T RA have been published.[5 9 10] Accumulation of such findings will elucidate actual situation and lead to better treatment strategies. We propose that we pay more

attention on patients with RA who do not meet the current criteria due to safety concerns.

Satoshi Takanashi , **Yuko Kaneko, Tsutomu Takeuchi**

Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan

Correspondence to Dr Tsutomu Takeuchi, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine Graduate School of Medicine, Shinjuku-ku, Tokyo, Japan; tsutake@z5.keio.jp

Handling editor Josef S Smolen

Contributors ST, YK and TT designed the study and wrote the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests YK has received grants or speaking fees from AbbVie, Astellas, Ayumi, Bristol-Myers Squibb, Chugai, Eisai, Eli Lilly, Hisamitsu, Jansen, Kissei, Pfizer, Sanofi, Takeda, Tanabe-Mitsubishi and UCB. TT has received research grants or speaking fees from Astellas Pharma, Bristol–Myers KK, Chugai Pharmaceutical Co, Daiichi Sankyo Co, Takeda Pharmaceutical Co, Teijin Pharma, AbbVie GK, Asahikasei Pharma Corp, Mitsubishi Tanabe Pharma, Astra Zeneca KK, Eli Lilly Japan KK, Novartis Pharma KK, Abbivie GK, Nipponkayaku Co, Janssen, Pharmaceutical KK, Taiho Pharmaceutical Co and Pfizer Japan.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Takanashi S, Kaneko Y, Takeuchi T. *Ann Rheum Dis* 2021;**80**:1491–1493.

Received 8 March 2021
Revised 28 April 2021
Accepted 29 April 2021
Published Online First 7 May 2021

Ann Rheum Dis 2021;**80**:1491–1493. doi:10.1136/annrheumdis-2021-220315

ORCID iDs
Satoshi Takanashi http://orcid.org/0000-0002-3607-2140
Tsutomu Takeuchi http://orcid.org/0000-0003-1111-8218

REFERENCES

1 Nagy G, Roodenrijs NMT, Welsing PMJ, *et al*. EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2021;80:31–5.
2 Smolen JS, Landewé RBM, Bijlsma JWJ. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;79:685–99.
3 Smolen JS, Aletaha D, Bijlsma JWJ, *et al*. Treating rheumatoid arthritis to target: recommendations of an international Task force. *Ann Rheum Dis* 2010;69:631–7.
4 Takanashi S, Kaneko Y, Takeuchi T. CDAI and DAS28 in the management of rheumatoid arthritis in clinical practice. *Ann Rheum Dis* 2020;79:671–4.
5 Takanashi S, Kaneko Y, Takeuchi T. Characteristics of patients with difficult-to-treat rheumatoid arthritis in real-world. *Rheumatology* 2021;2:keab209.
6 England BR, Sayles H, Mikuls TR, *et al*. Validation of the rheumatic disease comorbidity index. *Arthritis Care Res* 2015;67:865–72.
7 Dicker D, Nguyen G, Abate D, *et al*. Global, regional, and national age-sex-specific mortality and life expectancy, 1950–2017: a systematic analysis for the global burden of disease study 2017. *Lancet* 2018;392:1684–735.
8 Matthijssen XME, Huizinga TWJ, van der Helm-van Mil AHM. Increasing incidence of autoantibody-negative RA is replicated and is partly explained by an aging population. *Ann Rheum Dis* 2020. doi:10.1136/annrheumdis-2020-217609. [Epub ahead of print: 29 May 2021].
9 Roodenrijs NMT, van der Goes MC, Welsing PMJ. Difficult-To-Treat rheumatoid arthritis: contributing factors and burden of disease. *Rheumatology* 2020;17:keaa860.
10 Roodenrijs NMT, Hamar A, Kedves M, *et al*. Pharmacological and non-pharmacological therapeutic strategies in difficult-to-treat rheumatoid arthritis: a systematic literature review Informing the EULAR recommendations for the management of difficult-to-treat rheumatoid arthritis. *RMD Open* 2021;7:e001512.

Joint tenderness and ultrasound inflammation in DMARD-naïve patients with early rheumatoid arthritis

Tender joint count is part of most composite disease activity scores and treatment targets in rheumatoid arthritis (RA).[1] Joint tenderness could represent not only synovial inflammation in the absence of clinical swelling but also factors such as erosive damage and pain sensitisation.[2] Ultrasound examination can add information to the clinical evaluation of inflammation.

Joint tenderness did not reflect inflammatory activity when assessed by ultrasound in patients with established RA[3] but might be more related to inflammation in early arthritis.[4 5] We aimed to explore joint tenderness in DMARD-naïve patients with early RA and assess whether this finding was associated with ultrasound inflammation in the absence of swelling.

The analyses were performed using baseline data from the ARCTIC trial,[6] which included assessment of joint tenderness by Ritchie Articular Index and a 44-swollen joint count. The Ritchie Articular Index grades joint tenderness 0–3, with certain joints being treated as a single unit, for example, the metacarpal-phalangeal (MCP) joints. In the ultrasound examination, 32 joints were all dorsally scored semiquantitatively 0–3 for power Doppler (PD), with an ultrasound atlas for reference.[6] The wrists were predefined as the joint area of interest since they are commonly involved in RA and were assessed both clinically and by ultrasound. Additionally, in these joints, scoring of tenderness by Ritchie Articular Index could correspond to the more commonly used tender joint count. The presence of ultrasound inflammation was defined as a PD score of minimum one in any of the following areas: the radiocarpal joint, intercarpal joint, radioulnar joint and extensor carpi ulnaris tendon. We then selected only wrists that were clinically nonswollen and examined the association between joint tenderness and PD positivity in these joints by mixed logistic regression models with patient-specific intercept to adjust for within-patient dependencies. The analyses were repeated using generalised estimating equations for robustness. In secondary analyses, we explored tenderness of the MCP joints, but comparability with swelling and ultrasound findings were weakened by the lack of a regular tender joint count. The MCP1–5 had to be scored together as one unit for swelling and PD signal. The association between joint tenderness and grey-scale synovitis was also assessed.

Of the 230 patients, 61% were women, median (IQR) symptom duration of 5.6 (2.8, 10.2) months, swollen joint count of 10 (4, 15), joint tenderness by Ritchie Articular Index 7 (4, 13) and PD score of 7 (3, 14).[6] Of the 460 assessed wrists, 282/460 (61%) were clinically nonswollen. Of these, 38/282 (13%) were reported as tender (graded 1 or 2). The frequency of PD score ≥1 in the tender nonswollen wrists was 19/38 (50%) compared with 55/244 (23%) in the nontender nonswollen wrists. This corresponds to an OR of 4.70 (95% CI 1.62 to 13.62, p value <0.001) for PD signal in a tender nonswollen wrist compared with a nontender nonswollen wrist (figure 1). Similar results were found for grey-scale synovitis and for the nonswollen MCP joints. Of the 19 PD positive wrists, 11 had a total PD score of ≥2.

In conclusion, in nonswollen wrists, ultrasound PD activity was more frequent if the wrist was tender. A hypothetic explanation of this finding might be that tender joints at time of RA diagnosis reflect low-grade inflammation, which is not detectable clinically as swelling. In contrast to established RA, these patients with early RA had less joint damage, and central sensitisation due to long-lasting

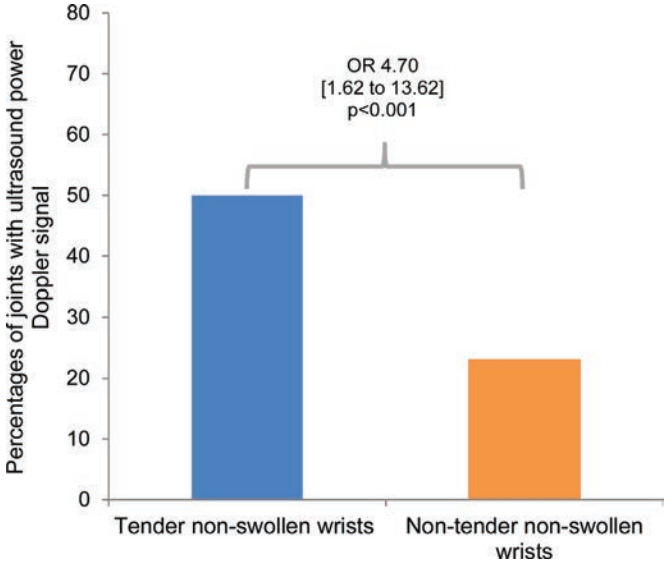


Figure 1 The frequency and OR of ultrasound power Doppler signal in tender vs non-tender non-swollen wrists.

inflammatory activation of pain fibres might not yet be an issue. A limitation of this study is the evaluation of tenderness by Ritchie Articular Index, reducing the number of joint areas available for analysis. The pathophysiology behind a tender joint in early RA should be further explored, and joint tenderness might deserve more attention when aiming for remission in early disease.

Nina Paulshus Sundlisater ,[1] **Anna-Birgitte Aga,**[1] **Inge Christoffer Olsen,**[2] **Hilde Berner Hammer** ,[1,3] **Till Uhlig** ,[1,3] **Désirée van der Heijde** ,[1,4] **Tore K Kvien,**[1,3] **Espen A Haavardsholm,**[1,3] **Siri Lillegraven**[1]

[1]Division of Rheumatology and Research, Diakonhjemmet Hospital, Oslo, Norway
[2]Clinical Trial Unit, Oslo University Hospital, Oslo, Norway
[3]Faculty of Medicine, University of Oslo, Oslo, Norway
[4]Rheumatology, Leiden University Medical Center, Leiden, Zuid-Holland, The Netherlands

Correspondence to Dr Nina Paulshus Sundlisater, Division of Rheumatology and Research, Diakonhjemmet Hospital, Oslo, Norway; ninasundlisater@gmail.com

Handling editor Josef S Smolen

Contributors All authors were involved in drafting the letter or revising it critically for important intellectual content and approved the final manuscript to be submitted and agreed to be accountable for all aspects of the work. Conception and design of the ARCTIC study: A-BA, ICO, HBH, TU, DvdH, TKK, SL and EAH. Acquisition of data: A-BA, HBH, TU and EAH. Analysis and interpretation of data: NPS, A-BA, ICO, HBH, TU, DvdH, TK, SL and EAH. EAH and SL are shared last authors.

Funding The ARCTIC study has received grants from the Norwegian Research Council, the South-East Health Region in Norway, the Norwegian Rheumatism Association, the Norwegian Women's public Health Association and unrestricted grant support from AbbVie, Pfizer, MSD, Roche and UCB. The funders of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Competing interests Dr NPS reports grants from The South-Eastern Norway Regional Health Authority, during the conduct of the study; Dr Aga reports personal fees from Abbvie, personal fees from Eli Lilly, personal fees from Novartis, personal fees from Pfizer, outside the submitted work; Dr ICO has nothing to disclose; Dr NBH reports personal fees from AbbVie, personal fees from Novartis, personal fees from Lilly, outside the submitted work; Dr TU reports personal fees from Lilly, personal fees from Novartis, outside the submitted work; Dr DvdHv reports personal fees from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Celgene, Cyxone, Daiichi, Eisai, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, UCB Pharma, outside the submitted work; and Director Imaging Rheumatology BV; Dr TKK reports personal fees from Amgen, personal fees from Celltrion, personal fees from Egis, personal fees from Evapharma, personal fees from Ewopharma, personal fees from Hikma, personal fees from Oktal, personal fees from Sandoz, personal fees from Sanofi, personal fees from Abbvie, personal fees from BMS, personal fees from MSD, personal fees from Pfizer, grants from UCB, personal fees from Biogen, personal fees from Eli Lilly, personal fees from Gilead, personal fees from Mylan, personal fees from Novartis, outside the submitted work; Dr EAH reports grants from The Research Council of Norway, grants from The South-Eastern Norway Regional Health Authority, during the conduct of the study; personal fees from Pfizer, from AbbVie, personal fees from Celgene, personal fees from Novartis, personal fees from Janssen, personal fees from Gilead, personal fees from Eli-Lilly, personal fees from UCB, outside the submitted work; Dr SL reports grants from The South-Eastern Norway Regional Health Authority, grants from The Research Council of Norway, grants from Norwegian Women's Public Health Association, grants from Norwegian Rheumatism Association, grants from AbbVie, grants from UCB Pharma, grants from Pfizer Inc, grants from MSD Norway, grants from Roche Norway, during the conduct of the study.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study was approved by an independent ethics committee (the regional Committee for Medical and Health research ethics south-east; reference number 2010/744).

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Paulshus Sundlisater N, Aga A-B, Olsen IC, *et al*. *Ann Rheum Dis* 2021;**80**:1493–1494.

Received 2 March 2021
Accepted 24 May 2021
Published Online First 3 June 2021

Ann Rheum Dis 2021;**80**:1493–1494. doi:10.1136/annrheumdis-2021-220265

ORCID iDs
Nina Paulshus Sundlisater http://orcid.org/0000-0002-1295-0172
Hilde Berner Hammer http://orcid.org/0000-0001-7317-8991
Till Uhlig http://orcid.org/0000-0002-6881-9552
Désirée van der Heijde http://orcid.org/0000-0002-5781-158X

REFERENCES

1 Smolen JS, Landewé RBM, Bijlsma JWJ, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;79:685–99.
2 Yunus MB. Editorial review: an update on central sensitivity syndromes and the issues of nosology and psychobiology. *Curr Rheumatol Rev* 2015;11:70–85.
3 Hammer HB, Michelsen B, Sexton J, *et al*. Swollen, but not tender joints, are independently associated with ultrasound synovitis: results from a longitudinal observational study of patients with established rheumatoid arthritis. *Ann Rheum Dis* 2019;78:1179–85.
4 Paulshus Sundlisæter N, Olsen IC, Aga A-B, *et al*. Predictors of sustained remission in patients with early rheumatoid arthritis treated according to an aggressive treat-to-target protocol. *Rheumatology* 2018;57:2022–31.
5 Gessl I, Popescu M, Schimpl V, *et al*. Role of joint damage, malalignment and inflammation in articular tenderness in rheumatoid arthritis, psoriatic arthritis and osteoarthritis. *Ann Rheum Dis* 2021;80:884–90.
6 Haavardsholm EA, Aga A-B, Olsen IC, *et al*. Ultrasound in management of rheumatoid arthritis: Arctic randomised controlled strategy trial. *BMJ* 2016;354:i4205.

Single cell and spatial transcriptomics in human tendon disease indicate dysregulated immune homeostasis

Tendinopathy; encompassing multifactorial tendon disorders characterised by pain and functional limitation remains a significant burden in musculoskeletal medicine.[1] Recent findings highlight a key role for immune mediated mechanisms in tendon disease supporting the concept that pivotal immunological and

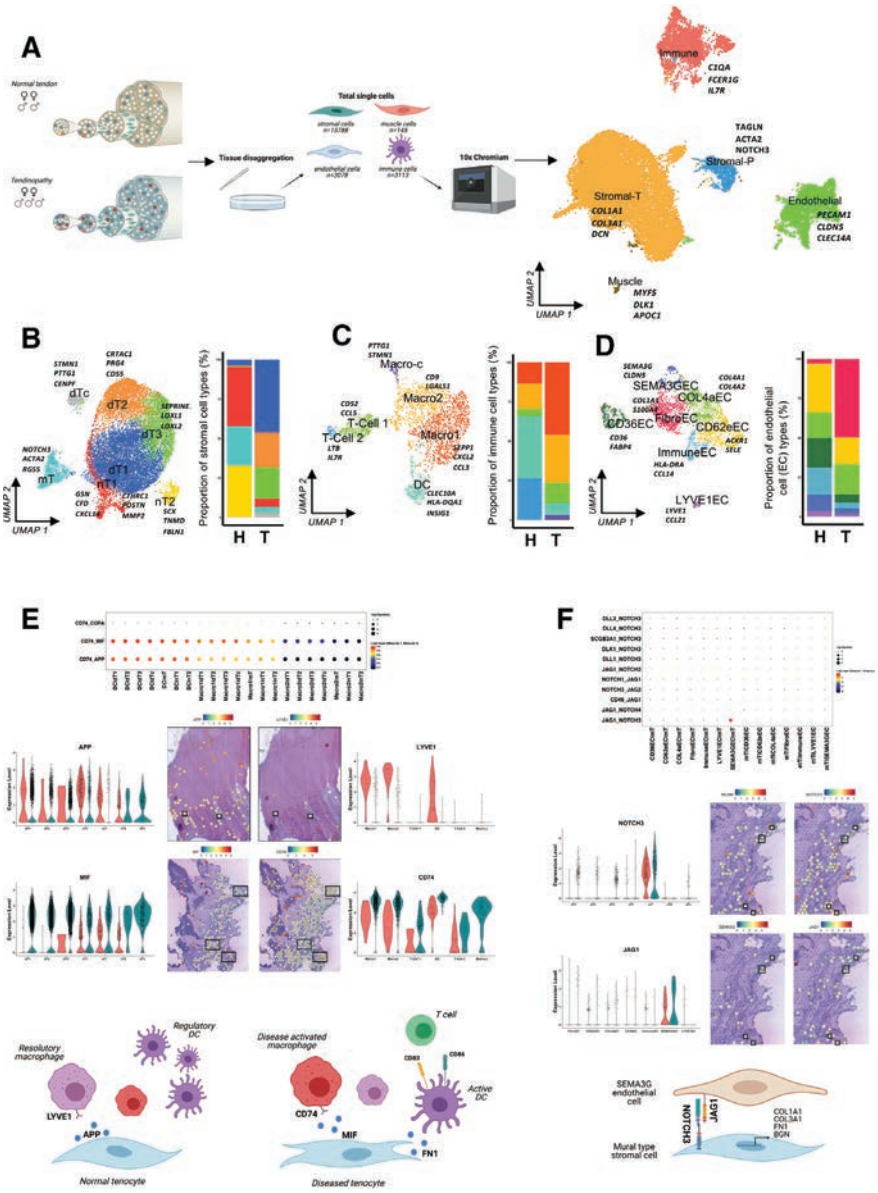


Figure 1 Cell composition and interactions of healthy and diseased human tendon. (A) Normal (n=4, human hamstring tendon) and diseased (tendinopathy, n=5, human supraspinatus tendon) human tendon were processed for single cell analysis using Chromium 10x 3′DEG chemistry. Infographic shows number of donors and cells sequenced. Uniform manifold approximation and projection (UMAP) embedding of 22 124 single cells delineating endothelial, immune, stromal tenocyte and stromal mural cells with marker genes. (B) Stromal cells of the tendon. UMAP embedding with gene markers and distribution of seven delineated stromal cell populations from human tendons; mural tenocyte (mT), normal tenocyte1 (nT1), normal tenocyte2 (nT2), diseased tenocyte1 (dT1), diseased tenocyte2 (dT2), diseased tenocyte3 (dT3) and diseased cycling tenocytes (dTc). (C) Immune cells of the tendon. UMAP embedding with gene markers and distribution of 6 delineated immune cell populations from human tendons; dendritic cells (DC), macrophage1 (Macro1), macrophage1 (Macro2), cycling macrophage (Macro-C), T-Cells1 (T-Cell1) and T-Cells2 (T-Cell2). (D) Endothelial cells (EC) of the tendon. UMAP embedding with gene markers and distribution of seven delineated EC populations from human tendons; CD36 high EC (CD36EC), E-Selectin EC (CD62eEC), collagen 4 vessel EC (COL4aEC), immune-like EC (ImmuneEC), LYVE1 positive EC (LYVE1EC) and SEMA3G positive EC (SEMA3GEC). (E) Tenocyte–immune interactions in tendon (n=3 healthy, vs 4 diseased). Predicted cell–cell interactions using CellphoneDB statistical framework on human tendon immune and stromal cells. Selected ligand receptor interactions showing *APP* and *MIF* ligand–receptor pairs in tendon stromal and immune cells. Mean of combined gene expression of interaction pairs (Log2 mean) and p value of specificity of interactions. Violin plots of *APP* and *MIF* expression in tendon stromal cells from healthy (pink) and diseased (green) tendon. Spatial expression (log2FC) of stromal *APP* and macrophage *LYVE1* in normal human tendon and stromal *MIF* and macrophage *CD74* in tendinopathic tendon visualised on 10x Genomics visium data, boxes highlight areas of coexpression. Violin plots of *LYVE1* and *CD74* expression in immune cells from healthy (pink) and diseased (green) tendon. Biorender infographic summarising tenocyte–immune cell interactions in tendon disease. (F) EC–tenocyte interactions in tendon. Predicted cell–cell interactions using CellphoneDB statistical framework on selected human tendon endothelial and stromal cells. Ligand–receptor interactions showing *NOTCH3* ligand–receptor pairs in tendon endothelial and stromal cells. Mean of combined gene expression of interaction pairs (Log2 mean) and p value of specificity of interactions. Violin plots of *NOTCH3* and *JAG1* expression in tendon stromal and ECs, respectively from healthy (pink) and diseased (green) tendon. Spatial expression (log2FC) of *NOTCH3* and *MCAM* from mural tenocytes and *SEMA3G* and *JAG1* from SEMA3GEC's in human diseased tendon visualised on 10x Genomics visium data, boxes highlight areas of coexpression. Biorender graphic of predicted SEMA3GEC and mT interaction in human tendon.

biomechanical factors conventionally associated with inflammatory rheumatic and musculoskeletal diseases (RMDs) are manifest in tendon.[2] Single cell technologies[3] (scRNAseq) are increasingly applied in rheumatology to identify key cellular phenotypes that drive disease pathogenesis. Despite efforts with small cell numbers and heterogenous tendon biopsies[4] there remains no detailed spatial tendon cell atlas to inform translational targeting. Herein, for the first time utilising scRNAseq and spatial transcriptomics (S_T), we carry out cell–cell interaction analysis to build an atlas of the dynamic cellular environment that drives the development of chronic human tendon disease.

In healthy (4 biopsies, n=3040 cells) and diseased (5 biopsies, n=19 084 cells) tendon we find a mix of endothelial, immune and stromal cells (figure 1A, online supplemental file 1). Each cell type group is present in disease and healthy tissue but with distinct quantitative and qualitative characteristics. Within stromal populations we identified 'mural type' stromal cells (figure 1B). Mural cells, which include pericytes, are possible progenitor cells in tendon[5] and interestingly, these cells are phenotypically similar to *NOTCH3* high mural cells described in rheumatoid arthritis (RA) synovium which can differentiate into fibroblasts following interactions with endothelial cells (ECs) via *JAG1*.[6] Cell–cell interaction and S_T analysis indicate a similar phenomenon could occur within tendinopathy between mural cells and *SEMA3G* ECs (figure 1F). In all diseased stromal cell populations, there was greater expression of genes for extracellular matrix proteins (eg, *COL1A1*, *COL3A1*, *FN1*, *BGN*) which is considered the hallmark feature of tendinopathy (online supplemental figure S2B). Furthermore, pathway analysis indicates stromal cell clusters shift from negative regulation of immune cell and cytokine responses in normal tendon (online supplemental figure S3A) to a state that promotes immune cell recruitment and activation along with cytokine secretion and response processes in diseased tendon (online supplemental figure S3B,C).

Seven subtypes of *PECAM1*+ ECs were found (figure 1D), including a population of *LYVE1*+ ECs that produce *CCL21* and have been shown to regulate dendritic cell (DC) migration.[7] Furthermore, *CCL21* is upregulated in these cells in tendinopathy (online supplemental figure S2C). DCs comprise the single largest immune cell population present in normal tendon (figure 1B). Intriguingly, DCs are also present in diseased tendon however, showing therein greater levels of DC activation and lower levels of *C1Q* genes (regulatory DC markers) (online supplemental figure S2D,E). The activation of DCs and subsequent T cell activation[8] in tendinopathy is further evidenced by pathway analysis of differentially upregulated genes in disease (online supplemental figure S3D,E). This activation may in part be due to increased matrix protein expression, such as *FN1*, which can activate DCs and resulting in alterations in T cell populations within tissue potentially contributing to mechanisms driving disease chronicity. Additionally, we found three populations of macrophages in diseased tendon, one of which, cycling macrophages (figure 1C, online supplemental figure S2A) is unique to diseased tissue. The transcript profile of macrophages in normal tendon most closely resembled tissue repair and debris clearance (figure 1E, online supplemental figure S2D). Within normal tendon we found *APP* expression in tenocytes which can induce a resolution promoting phenotype in macrophages. However, *APP* expression was reduced in the stromal compartment in disease coinciding with diminished expression of *LYVE1* within diseased tissue macrophages (figure 1E, online supplemental figure S2D). These macrophage subsets have recently been associated with RA remission and we postulate the phenotypic drift away from this phenotype promotes aberrant tissue repair and attendant tendinopathy.[9]

Further evidence suggesting that the stromal environment may induce inflammatory changes comprises increased expression of *MIF* (figure 1E, online supplemental figure S2B) in diseased tenocytes that can induce proinflammatory effects via its receptor *CD74*, which is also upregulated in macrophages from diseased tendon (figure 1E, online supplemental figure S2C). S_T generated indicative data from cell–cell interaction analysis suggests stromal induced immune regulation. As such, we postulate the primary role of the immune compartment within the tendon is to regulate and resolve damage; however, following cumulative microtrauma the fundamental process of debris removal and matrix repair initiated by tenocytes could lead to positive amplification of the immune compartment. We further propose that within diseased tendon immune homoeostasis may become imbalanced and activated immune cells, primed by both endothelial and stromal cells, promote a cycle of inflammation and aberrant tissue repair. The inflammatory environment, including cytokine pathways that are unequivocally demonstrated in this preliminary tendon atlas, have been targeted to yield potent immunological interventions in a range of inflammatory RMDs—the potential to target and investigate these pathways in human tendon disease is now compelling.

Moeed Akbar ,[1] **Lucy MacDonald** ,[1,2] **Lindsay A N Crowe**,[1] **Konstantin Carlberg** ,[3] **Mariola Kurowska-Stolarska** ,[1,2] **Patrik L Ståhl**,[3] **Sarah J B Snelling**,[4] **Iain B McInnes**,[1,2] **Neal L Millar** [1]

[1]Institute of Infection, Immunity and Inflammation, College of Medical Veterinary and Life Sciences, University of Glasgow, Glasgow, UK
[2]Research into Inflammatory Arthritis Centre Versus Arthritis (RACE), University of Glasgow, Glasgow, UK
[3]Science for Life Laboratory, Dept. of Gene Technology, KTH Royal Institute of Technology, Solna, Sweden
[4]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

Correspondence to Mr Neal L Millar, Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow G12 8TA, UK; neal.millar@glasgow.ac.uk

Handling editor Josef S Smolen

Twitter Neal L Millar @tendonglasgow

Acknowledgements We thank the CZI Tendon Seed Network for helpful discussions when preparing this manuscript for publication.

Contributors MA, LM and NM conceived and designed the experiments. MA, LM and KC performed experiments. IBM, NM, LANC, PS and SJBS provided expert advice. All authors analysed the data. MA, LANC, IBM and NM wrote the paper.

Funding This work was funded by the Medical Research Council (MR/R020515/1). SJBS was funded by the NIHR Oxford Biomedical Research Centre.

Competing interests KC and PS are scientific consultants to 10x Genomics.

Patient consent for publication Not required.

Ethics approval All procedures and protocols were approved by the Ethics Committee under the approval number West of Scotland REC (REC14/WS/1035) with informed consent obtained and carried out in accordance with standard operative procedures.

Provenance and peer review Not commissioned; externally peer reviewed.

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220256).

To cite Akbar M, MacDonald L, Crowe LAN, *et al*. *Ann Rheum Dis* 2021;**80**:1494–1497.

Received 1 March 2021
Accepted 5 May 2021
Published Online First 17 May 2021

Ann Rheum Dis 2021;**80**:1494–1497. doi:10.1136/annrheumdis-2021-220256

ORCID iDs
Moeed Akbar http://orcid.org/0000-0002-6923-4724
Lucy MacDonald http://orcid.org/0000-0001-7727-3873
Konstantin Carlberg http://orcid.org/0000-0002-1774-6058
Mariola Kurowska-Stolarska http://orcid.org/0000-0003-2124-7777
Neal L Millar http://orcid.org/0000-0001-9251-9907

REFERENCES

1 Millar NL, Silbernagel KG, Thorborg K, *et al*. Tendinopathy. *Nat Rev Dis Primers* 2021;7:1.
2 Gracey E, Burssens A, Cambré I, *et al*. Tendon and ligament mechanical loading in the pathogenesis of inflammatory arthritis. *Nat Rev Rheumatol* 2020;16:193–207.
3 Cheung P, Khatri P, Utz PJ, *et al*. Single-cell technologies - studying rheumatic diseases one cell at a time. *Nat Rev Rheumatol* 2019;15:340–54.
4 Kendal AR, Layton T, Al-Mossawi H, *et al*. Multi-Omic single cell analysis resolves novel stromal cell populations in healthy and diseased human tendon. *Sci Rep* 2020;10:13939.
5 De Micheli AJ, Swanson JB, Disser NP, *et al*. Single-Cell transcriptomic analysis identifies extensive heterogeneity in the cellular composition of mouse Achilles tendons. *Am J Physiol Cell Physiol* 2020;319:C885–94.
6 Wei K, Korsunsky I, Marshall JL, *et al*. Notch signalling drives synovial fibroblast identity and arthritis pathology. *Nature* 2020;582:259–64.
7 Murphy PM. Double duty for CCL21 in dendritic cell trafficking. *Immunity* 2010;32:590–2.
8 Garcia-Melchor E, Cafaro G, MacDonald L, *et al*. Novel self-amplificatory loop between T cells and tenocytes as a driver of chronicity in tendon disease. *Ann Rheum Dis* 2021;80:1075–85.
9 Alivernini S, MacDonald L, Elmesmari A, *et al*. Distinct synovial tissue macrophage subsets regulate inflammation and remission in rheumatoid arthritis. *Nat Med* 2020;26:1295–306.

Effects of face masks on oxygen saturation and functional measures in patients with connective tissue disorder-associated interstitial lung disease

Face masks are a first-line defence against the COVID-19 pandemic.[1] Concerns about face masks reducing oxygen saturation (SpO_2) have been negated by controlled studies in healthy individuals.[2 3] Universal masking must be followed without exceptions. However, persons with pre-existing cardiorespiratory diseases like interstitial lung diseases (ILD) have limited functional reserves. We explored the effects of face masks in patients with connective tissue disease (CTD)-associated ILD (CTD-ILD).

Patients between 18 and 75 years of age with high-resolution CT (HRCT)-proven CTD-ILD and with Medical Research Council scale grades 1–3 dyspnoea and forced vital capacity (FVC) of less than 70% were included in this crossover trial. If FVC was >70%, patients were included only if the extent of involvement on HRCT was more than 20% of the lung. Patients requiring oxygen supplementation and with myositis or lower limb pain were excluded. Initial SpO_2 was recorded and a standard 6 min walk test (6MWT) was carried out with and then without a standard three-layer surgical face mask. Adequate precautions were taken to prevent the spread of COVID-19 during the tests. Distance covered during the 6MWT was the primary outcome measure. The secondary outcome measures were drop in SpO_2, time for saturation to return to baseline and dyspnoea measured on the Borg Dyspnoea Scale. Considering a mean (SD) 6MWT distance of 250 (53) m and a minimal clinically significant difference of 10% reduction, with alpha of 0.05 and power of 80%, the sample size was calculated at 36. The trial was registered as CTRI/2021/01/030234 in the Clinical Trial Registry of India (CTRI). Paired Student's t-test, Wilcoxon signed-rank test and McNemar test were performed using SPSS V.23.0.

After block randomisation, 18 patients were assessed without masks on first and 18 with masks on first. All 36 patients (online supplemental table 1) completed 6MWT both with and without masks. The participants covered a mean of 12.9 m (95% CI 4.5 to 21.4; p=0.004) lesser distance and had a larger drop in saturation (p=0.03) while on masks than when not wearing masks. The number of persons who had any rise in the Borg Dyspnoea Scale during peak activity was significantly different (table 1). A decline in SpO_2 of 2% or more occurred in 14 participants without masks and in 19 with masks (p=0.3; Fisher's exact test).

Thus, the use of face masks reduced functional capacity and SpO_2 during activity in patients with CTD-ILD. Even with the

Table 1 Parameters during 6MWT in 36 patients with connective tissue disorder-associated interstitial lung diseases with and without face masks

	Without face masks	With face masks	Test for significance*, p value
Distance covered (m)	264.3 (44.1)	251.4 (51.4)	0.004
Baseline oxygen saturation (%)	97.4 (2.4)	97 (2.8)	0.15
Oxygen saturation (%) at completion of 6MWT	94.4 (5.7)	92 (6.5)	0.03
Drop in oxygen saturation (%)	3.0 (3.8)	4.1 (4.5)	0.03
Time taken for recovery of oxygen saturation (s)	35.4 (65.2)	67.1 (78.0)	0.002
Number who had rise in Borg Dyspnoea Scale by at least single unit	21	30	0.008

Data presented as mean (SD).
*Student's t-test for parametric data (distance covered), Wilcoxon signed-rank test for non-parametric data (rest) and McNemar test for proportions.
6MWT, 6 min walk test.

roll-out of COVID-19 vaccines around the world, masks remain the standard of care. We strongly advocate the use of masks for all, including patients with ILD, who may be at higher risk if they develop COVID-19. Although only CTD may not confer additional risk for COVID-19, the presence of ILD increases the risk of severe disease.[4]

Functional MRI studies have shown carbon dioxide retention while wearing face mask alters brain oxygenation patterns without affecting task activation in healthy subjects.[5] Other studies which have shown no effect of masks have been on elderly participants without any active exertion[2] or on young adults during exercise.[3] However, these studies had smaller numbers and did not evaluate patients with lung disease during exertion. Conversely, it should also be kept in mind that dyspnoea is a subjective feeling and patients with respiratory diseases may be subconsciously biased against masks.[6] This study should not be misinterpreted as implying face masks should not be used in patients with CTD-ILD.

Our limitations include the use of surgical mask only. However, this was to standardise the experiment. We expect other types of masks and idiopathic ILD to behave similarly.

We reiterate that it is quintessential for these patients to continue wearing masks. However, patients with ILD, their caregivers and physicians should know that functional capacity may be reduced with masks. Patients should limit physical exertion while wearing masks.

This study should not be misinterpreted as implying face masks should not be used by patients with CTD-ILD because this would risk COVID-19 infection, which would be very much detrimental to such patients. Continuous use of masks as well as other COVID-19 protocols is secondary to none.

Anuroopa Vijayan,[1,2] Sakir Ahmed ,[3] Sneha Joseph,[2] Aswathy Sukumaran,[2] Subin Ahmed,[4] Padmanabha Shenoy [1,2]

[1]Rheumatology, Sree Sudheendra Medical Mission Hospital, Kochi, Kerala, India
[2]Rheumatology, Centre for Arthritis and Rheumatism Excellence, Kochi, India
[3]Clinical Immunology and Rheumatology, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India
[4]Pulmonary Medicine, Renai Medicity Multi Super Specialty Hospital, Kochi, Kerala, India

Correspondence to Dr Padmanabha Shenoy, Rheumatology, Sree Sudheendra Medical Mission Hospital, Kochi 682018, Kerala, India; drdpshenoy@gmail.com

Handling editor Josef S Smolen

Contributors Conceptualisation: PS. Methodology: PS, SaA,SuA, AV, SJ. Writing-original draft: SaA. Writing-review and editing: all authors. All authors have approved the final manuscript and take full responsibility for the integrity of the data and the content of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The trial was approved by the Sree Sudheendra Medical Mission Hospital Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220230).

To cite Vijayan A, Ahmed S, Joseph S, *et al*. *Ann Rheum Dis* 2021;**80**:1497–1498.

Received 23 February 2021
Revised 29 April 2021
Accepted 29 April 2021
Published Online First 10 May 2021

Ann Rheum Dis 2021;**80**:1497–1498. doi:10.1136/annrheumdis-2021-220230

ORCID iDs
Sakir Ahmed http://orcid.org/0000-0003-4631-311X
Padmanabha Shenoy http://orcid.org/0000-0002-7666-1361

REFERENCES

1 Chu DK, Akl EA, Duda S, *et al*. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. *Lancet* 2020;395:1973–87.
2 Chan NC, Li K, Hirsh J. Peripheral oxygen saturation in older persons wearing nonmedical face masks in community settings. *JAMA* 2020;324:2323–4.
3 Shaw K, Butcher S, Ko J, *et al*. Wearing of cloth or disposable surgical face masks has no effect on vigorous exercise performance in healthy individuals. *Int J Environ Res Public Health* 2020;17:8110.
4 Ahmed S, Gasparyan AY, Zimba O. Comorbidities in rheumatic diseases need special consideration during the COVID-19 pandemic. *Rheumatol Int* 2021;41:243–56.
5 Law CSW, Lan PS, Glover GH. Effect of wearing a face mask on fMRI BOLD contrast. *Neuroimage* 2021;229:117752.
6 Soriano JB, Anzueto A, Bosnic Anticevich S, *et al*. Face masks, respiratory patients and COVID-19. *Eur Respir J* 2020;56. doi:10.1183/13993003.03325-2020. [Epub ahead of print: 12 Nov 2020].

Broad clinical spectrum of SARS-CoV-2-associated inflammatory joint disease in adults: a report of 35 cases from the COVID-19 & Autoimmune Systemic Disease Italian study group

Large cohort studies demonstrated that a sizeable proportion of patients with acute COVID-19 present with symptoms or signs of rheumatological interest such as arthralgia/myalgia, inflammatory skin lesions and/or autoantibodies positivity.[1] Subsequent clinical observations disclosed the existence of a post-acute COVID-19 syndrome, characterised by a large constellation of manifestations including fatigue, arthralgia and myalgia.[2] The potential role of viruses in the development of rheumatic diseases is well recognised, either as causative agents or antigenic triggers for the ensuing development of autoimmunity.[3] Consistent with these premises, from the earliest phases of the pandemic, inflammatory musculoskeletal manifestations following COVID-19 have been described in isolated case reports although no systematically collected cohorts are still available to unveil the clinical spectrum of post-COVID-19 arthritis.[4]

To contribute to shed light on this field, in December 2020, we built a web-based survey platform and invited all members of our study group to submit cases of inflammatory joint disease and onset within 8 weeks from a confirmed

Table 1 Clinical features and laboratory/imaging findings in patients with SARS-CoV-2-associated inflammatory joint disease

	Whole cohort (n=35)	Early onset (≤2 weeks) (n=12)	Late onset (>2 weeks) (n=23)	P value early vs late onset
Age, years	52.4±13.3	50.3±9.4	53.5±15.0	0.44
Female sex, n (%)	23 (65.7)	7 (58.3)	16 (69.6)	0.71
Current smokers, n (%)	6 (17.1)	1 (8.3)	5 (21.7)	0.64
Symptomatic COVID-19, n (%)	29 (82.9)	12 (100)	17 (73.9)	0.07
COVID-19 symptoms				
Fever, n (%)	26 (74.3)	10 (83.3)	16 (69.6)	0.45
Cough, n (%)	17 (48.6)	5 (41.7)	12 (52.2)	0.72
Dyspnoea, n (%)	8 (22.9)	4 (33.3)	4 (17.4)	0.40
Arthralgia and/or myalgia, n (%)	22 (62.9)	11 (91.7)	11 (47.8)	0.01
Taste and/or smell loss, n (%)	8 (22.9)	4 (33.3)	4 (17.4)	0.40
Severe COVID-19*, n (%)	3 (8.6)	1 (8.3)	2 (8.7)	1.00
Evidence of SARS-CoV-2 infection				
RT-PCR on nasopharyngeal swab, n (%)	32 (91.4)	12 (100)	20 (86.9)	0.54
SARS-CoV-2 specific IgM, n (%)	3 (8.6)	0 (0)	3 (13.0)	0.27
COVID-19 treatment				
Paracetamol/NSAIDs, n (%)	21 (60.0)	10 (83.3)	11 (47.8)	0.07
Glucocorticoids, n (%)	11 (31.4)	6 (50)	5 (21.7)	0.13
Hydroxychloroquine, n (%)	1 (2.9)	1 (8.3)	0 (0)	0.34
Low-molecular-weight heparin, n (%)	5 (14.3)	1 (8.3)	4 (17.4)	0.64
Antibiotics and/or antivirals, n (%)	4 (11.4)	0 (0)	4 (17.4)	0.27
Time between COVID-19 diagnosis and arthritis onset, days	23.7±17.0	6.3±3.3	32.9±13.7	<0.0001
Pattern of joint involvement				
Asymmetric monoarthritis or oligoarthritis, n (%)	18 (51.4)	3 (25.0)	15 (65.2)	0.03
RA-like polyarthritis, n (%)	7 (20.0)	5 (41.7)	2 (8.7)†	0.03
PMR-like, n (%)	4 (11.4)	1 (8.3)	3 (13.0)‡	1.00
Predominantly axial, n (%)	4 (11.4)	3 (25.0)§	1 (4.3)	0.11
Enthesitis, n (%)	2 (5.7)	0 (0)	2 (8.7)	0.54
US or MRI confirmed inflammation, n (%)	21 (60.0)	5 (41.7)	16 (69.6)	0.15
RF positive, n (%)¶	1 (3.4)	1 (12.5)	0 (0)	0.27
ACPA positive, n (%)¶	0 (0)	0 (0)	0 (0)	N/A
ANA positive, n (%)¶	6 (22.2)	2 (25.0)	4 (21.0)	1.00
HLA-B27 positive, n (%)¶	1 (7.7)	0 (0)	1 (9.1)	1.00
ESR, mm/h	31.3±18.3	24.9±17.8	34.6±18.1	0.14
CRP, mg/dL	2.34±2.58	2.74±2.50	2.14±2.65	0.51
Treatment				
NSAIDs, n (%)	25 (71.4)	9 (75.0)	16 (69.6)	1.00
Glucocorticoids, n (%)	16 (45.7)	5 (41.7)	11 (47.8)	1.00
DMARDs, n (%)**	6 (17.1)	2 (16.7)	4 (17.4)	1.00
Follow-up duration, weeks	10.4 9.8	10.3±11.2	10.5±9.2	0.95
Outcome				
Improved, n (%)	10 (28.6)	4 (33.3)	6 (26.1)	0.71
Recovered, n (%)	8 (22.9)	2 (16.7)	6 (26.1)	0.68
Relapsed, n (%)	4 (11.4)	1 (8.3)	3 (13.0)	1.00
Active, n (%)	12 (34.4)	5 (41.7)	7 (30.4)	0.71
N/A, n (%)	1 (2.9)	0 (0)	1 (4.3)	1.00

*Severe COVID-19 was defined as previously described as the presence of dyspnoea, respiratory rate of 30 or more breaths/min, blood oxygen saturation of 93% or less and ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2) of less than 300 mm Hg, or infiltrates in more than 50% of the lung field (JAMA 2020 Apr 7;323(13):1239–42).

†Two out of two patients had polyarthritis affecting predominantly large joints.

‡One out of three patients with PMR presented with concurrent giant cell arteritis.

§Two out of three patients had concurrent peripheral involvement of metacarpophalangeal and proximal interphalangeal joints.

¶RF and ACPA were obtained in 29 out of 35 patients (8 in early onset and 21 in late onset group, respectively), ANA in 27 out of 35 patients (8 in early onset and 19 in late onset group, respectively), HLA-B27 in 13 out of 35 patients (2 in early onset and 11 in late group, respectively).

**Either methotrexate, sulfasalazine or hydroxychloroquine.

ACPA, anticitrullinated protein antibody; ANA, antinuclear antibodies; CRP, C reactive protein; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; N/A, not available; NSAIDs, non-steroidal anti-inflammatory drugs; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; RF, rheumatoid factor; RT-PCR, real-time PCR; US, ultrasonography.

SARS-CoV-2 infection (demonstrated either by reverse transcription PCR on nasopharyngeal swab or SARS-CoV-2-specific IgM antibodies) encountered during routine clinical practice from 31 January 2020 and up to 31 March 2021. Exclusion criteria were a history of any inflammatory rheumatic disease or psoriasis. General characteristics of the patients are reported in table 1.

The clinical spectrum of rheumatic manifestations spanned from asymmetric monoarthritis or oligoarthritis (51%) to rheumatoid arthritis (RA)-like symmetric polyarthritis of the small joints (20%). Furthermore, 11% of cases presented with predominantly axial involvement (inflammatory back pain and evidence of sacroiliitis/spondylitis on MRI) and polymyalgia rheumatica-like involvement of shoulder and hip girdles, respectively. Finally, two patients had isolated peripheral enthesitis. Autoantibodies were usually absent, except for non-specific antinuclear antibody positivity encountered in 22% of cases. The overall course was relatively benign with half of the patients experiencing remission of the symptoms after treatment with non-steroidal anti-inflammatory drugs, glucocorticoids or disease-modifying antirheumatic drugs. Further, we stratified patients according to the delay between COVID-19 and arthritis onset as early (≤2 weeks) or late (>2 weeks), on the basis of the approximated average duration of COVID-19 symptoms in the outpatient setting. Strikingly, we observed a clustering of RA-like pattern in patients with early arthritis onset; the only two cases of oligoarthritis in this subset affected small joints of hands and wrist; furthermore, two out of three patients with axial involvement had also pain in metacarpophalangeal and proximal interphalangeal joints.

We hypothesise that such a clustering may suggest different underlying pathophysiological mechanisms. On the one hand, the earlier RA-like pattern is similar to what observed in other virus-associated arthritis, such as parvovirus B19 or hepatitis C virus-related arthritis.[5] On the other hand, the monoarticular or oligoarticular forms resemble the clinical features of reactive arthritis. For this reason, we speculate that the arthritogenic potential of SARS-CoV-2 may be broad and exploit both direct viral and indirect dysimmune mechanisms. Unfortunately, our report is affected by the intrinsic limitations of a real-life case series. Synovial fluid analysis was not carried out and thus it is not possible to exclude acute illness-triggered crystal arthritis[6] although not having performed joint aspiration implies that the clinical probability was considered low according to rheumatologist's clinical judgement. Moreover, no attempt to isolate SARS-CoV-2 RNA in synovial samples was made. In conclusion, despite our data do not allow to draw firm conclusions regarding the causative role of SARS-CoV-2 in the development of arthritis, they represent a fascinating hypothesis-generating basis for further systematic studies aimed at elucidating mechanisms behind this new entity.

Francesco Ursini,[1,2] Piero Ruscitti ,[3] Salvatore D'Angelo ,[4] Fabio Cacciapaglia ,[5] Rossella De Angelis,[6] Corrado Campochiaro,[7] Francesco Caso,[8] Maria De Santis,[9] Ilenia Di Cola,[3] Simone Parisi ,[10] Vincenzo Raimondo,[11] Giuseppina Abignano ,[4] Luisa Costa,[8] Jacopo Ciaffi,[1] Lorenzo Dagna,[7] Annamaria Iagnocco,[12] Florenzo Iannone ,[13] Riccardo Meliconi ,[1,2] Roberto Giacomelli,[14] Clodoveo Ferri [11,15]

[1]Medicine & Rheumatology Unit, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy
[2]Department of Biomedical and Neuromotor Sciences (DIBINEM), Alma Mater Studiorum University of Bologna, Bologna, Italy
[3]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila Faculty of Medicine and Surgery, L'Aquila, Italy
[4]Rheumatology Institute of Lucania (IReL) and Rheumatology Department of Lucania, Regional Hospital San Carlo, Potenza, Italy
[5]Rheumatology Unit, Department of Emergence Medicine and Transplantation (DETO), Università degli Studi di Bari Facoltà di Medicina e Chirurgia, Bari, Italy
[6]Rheumatology Clinic, Department of Clinical and Molecular Sciences, Polytechnic University of Marche School of Medicine and Surgery, Ancona, Italy
[7]Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), IRCCS Ospedale San Raffaele, Milano, Italy
[8]Rheumatology Unit, Department of Clinical Medicine and Surgery, Federico II University Hospital, Napoli, Italy
[9]Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Rozzano, Italy
[10]Rheumatology Unit, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino, Italy
[11]Rheumatology Unit, Rheumatology Hospital "Madonna dello Scoglio", Cotronei, Italy
[12]Academic Rheumatology Centre, Università degli Studi di Torino, Torino, Italy
[13]Rheumatology Unit, Department of Emergency Medicine and Transplantation, Università degli Studi di Bari Aldo Moro, Bari, Italy
[14]Rheumatology and Immunology Unit, Department of Medicine, Campus Bio-Medico University, Roma, Italy
[15]Rheumatology Unit, School of Medicine, Università degli Studi di Modena e Reggio Emilia Facoltà di Medicina e Chirurgia, Modena, Italy

Correspondence to Professor Clodoveo Ferri, Rheumatology Clinic 'Madonna dello Scoglio', Cotronei, Italy; clferri@unimore.it

Handling editor Josef S Smolen

Contributors FU and CF conceived the work and drafted the manuscript. All authors contributed to the acquisition and interpretation of data and to the critical revision of the draft. All authors approve the final version of the manuscript and agree to be accountable for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Ursini F, Ruscitti P, D'Angelo S, *et al*. *Ann Rheum Dis* 2021;**80**:1498–1501.

Received 19 April 2021
Accepted 10 May 2021
Published Online First 26 May 2021

Ann Rheum Dis 2021;**80**:1498–1501. doi:10.1136/annrheumdis-2021-220606

ORCID iDs
Piero Ruscitti http://orcid.org/0000-0003-3487-8551
Salvatore D'Angelo http://orcid.org/0000-0002-7442-1110
Fabio Cacciapaglia http://orcid.org/0000-0001-7479-4462
Simone Parisi http://orcid.org/0000-0003-4496-8315
Giuseppina Abignano http://orcid.org/0000-0002-1479-0133
Florenzo Iannone http://orcid.org/0000-0003-0474-5344
Riccardo Meliconi http://orcid.org/0000-0001-5216-5219
Clodoveo Ferri http://orcid.org/0000-0002-0840-5817

REFERENCES

1 Ciaffi J, Meliconi R, Ruscitti P, *et al*. Rheumatic manifestations of COVID-19: a systematic review and meta-analysis. *BMC Rheumatol* 2020;4:65.
2 Nalbandian A, Sehgal K, Gupta A, *et al*. Post-Acute COVID-19 syndrome. *Nat Med* 2021;27:601–15.
3 Calabrese LH, Naides SJ. Viral arthritis. *Infect Dis Clin North Am* 2005;19:963–80.
4 Gasparotto M, Framba V, Piovella C, *et al*. Post-COVID-19 arthritis: a case report and literature review. *Clin Rheumatol* 2021. doi:10.1007/s10067-020-05550-1. [Epub ahead of print: 15 Feb 2021].

5 Vassilopoulos D, Calabrese LH. Virally associated arthritis 2008: clinical, epidemiologic, and pathophysiologic considerations. *Arthritis Res Ther* 2008;10:215.
6 Zleik N, Elfishawi MM, Kvrgic Z, *et al*. Hospitalization increases the risk of acute arthritic flares in gout: a population-based study over 2 decades. *J Rheumatol* 2018;45:1188–91.

Tocilizumab in VEXAS relapsing polychondritis: a single-center pilot study in Japan

Recently, a rare severe autoinflammatory disease vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome caused by somatic variants in the *UBA1* gene was discovered.[1] We reported the clinical features of eight relapsing polychondritis (RP) patients with *UBA1* variants, six of which were accompanied by myelodysplastic syndrome (MDS).[2]

The clinical features of VEXAS syndrome are heterogeneous, including high-grade fever, polychondritis, large vessel vasculitis, skin eruptions, arthritis, thrombosis, scleritis and serositis, which require intensive immunosuppressive agents. Most of our patients before this study had received high doses of prednisolone (PSL) and cytotoxic immunosuppressants including methotrexate, cyclophosphamide and azathioprine.[1 2] However, even with concomitant immunosuppressant treatment, PSL tapering often led to a relapse of high-grade fever and skin rash in these patients; therefore, ≥20 mg oral PSL was required in most cases, resulting in frequent hospitalisation and death due to opportunistic infections. In addition, many cases of VEXAS syndrome already have MDS at the time of diagnosis, and cytotoxic immunosuppressive agents should be avoided or reduced in dose because they might cause further cytopenia.

Tocilizumab (TCZ), an anti-interleukin (IL)-6 receptor antagonist approved for the treatment of inflammatory diseases, such as rheumatoid arthritis and giant cell arteritis, may be useful in managing severe inflammation in VEXAS–RP and preserving the cumulative dose of PSL, which causes organ damage. Previous papers reported high IL-6 transcriptome signatures not only in zebrafish but also in $CD14^+$ isolated monocytes from patients with VEXAS,[1] suggesting IL-6 inhibition could be beneficial. Indeed, previous studies on VEXAS syndrome cases reported the use of TCZ.[1–5] However, the clinical course after TCZ administration has not been reported in detail. Here, we report our experience with TCZ in patients with VEXAS–RP.

Three cases of newly diagnosed VEXAS–RP (all male, median age 66.6 years) between August and December 2020 were included in the analysis. The details of their genetic and clinical characteristics were reported previously.[2] The dosage of TCZ was 8 mg/kg intravenously every 2 weeks in RP13 and 162 mg subcutaneously every week in RP15 and RP16.

The clinical courses before and after administration of TCZ are summarised in table 1. The observation period was 5–8 months. Two of the three patients showed afebrile status after TCZ treatment and had a reduced PSL dose. In RP16, rashes recurred after PSL was reduced to 17.5 mg and fever relapsed at 12.5 mg. After fever flare-up, TCZ was changed to intravenous administration and PSL was increased to 30 mg. The serum cytokine profile of these patients showed that baseline serum IL-6 levels did not correlate with the efficacy of TCZ treatment, and high serum proinflammatory cytokine levels, such as IL-18, persisted more than 4 months after induction, even in patients who appeared to have responded to TCZ, suggesting that TCZ alone may not be able to suppress the underlying inflammation of VEXAS syndrome (table 1 and online supplemental table 1). Fractional abundance (equivalent to allele frequencies) of *UBA1* mutation of RP16 who relapsed had the longest disease duration was highest with nearly 90% in the peripheral blood (table 1).

Table 1 Clinical features of the VEXAS-RP patients treated with tocilizumab

Patient ID	RP13	RP15	RP16
Sex	Male	Male	Male
Age of onset (years)	66.3	73.5	66.6
Time form onset to VEXAS diagnosis (months)	3	2	30
UBA1 variants p.Met41	c.122T>C: p.Met41Thr	c.122T>C: p.Met41Thr	c.121A>C: p.Met41Leu
UBA1 variant fractional abundance*	22.4 %	68.8 %	87.1 %
Clinical findings	High-grade fever, skin rash, RP, scleritis, peritonitis, pericarditis, meningitis	High-grade fever, skin rash, RP, macrocytic anaemia	High-grade fever, skin rash, GCA, RP, MDS, DVT, scleritis, airway involvement
Treatments before TCZ	PSL	PSL, MTX	PSL, AZP, colchicine
Concomitant treatments with TCZ	PSL	PSL	PSL, colchicine
Symptoms existed at TCZ induction‡	High-grade fever, myalgia, headache	Low-grade fever	High-grade fever, skin rash, RBC and PLT transfusion dependence
PSL dose at diagnosis of VEXAS syndrome	30 mg	50 mg	50 mg
PSL dose before TCZ administration	9 mg	22.5 mg	30 mg
PSL dose at last visit	3 mg	13.5 mg	30 mg
Hb level before TCZ administration	119 g/L	118 g/L	†74 g/L
Hb level at last visit	116 g/L	121 g/L	†91 g/L
Adverse events over 4 months	Herpes zoster	None	Herpes zoster, drug eruption
Symptoms existed after 4 months	None	None	Arthritis, RBC transfusion dependence, fever, skin rash, pulmonary infiltration
Serum IL-6 levels before TCZ	10.49 pg/mL	693.33 pg/mL	22.13 pg/mL
Observation period after TCZ	8 months	5 months	5 months

*Fractional abundance of peripheral blood detected by dd-PCR.[2]
†Hb level before RBC transfusion.
‡Symptoms existed during the past 1 month before TCZ induction.

AZP, azathioprine; DVT, deep vein thrombosis; GCA, giant-cell arteritis; Hb, haemoglobin; IL, interleukin; MDS, myelodysplastic syndrome; MTX, methotrexate; PLT, platelets; PSL, prednisolone; RBC, red blood cells; RP, relapsing chondritis; TCZ, tocilizumab; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

Two patients had herpes zoster infection, one of whom required hospitalisation. However, after 1-week treatment with antiviral therapy, both patients restarted TCZ. Our patients did not develop intestinal perforation as previously reported during the follow-up period.[5]

This report had several limitations. First, there was selection bias due to the small number of patients. Second, the observation period was only 5–8 months, and the long-term efficacy and side effects of TCZ after further reduction of PSL are unknown. Furthermore, due to the retrospective observational nature of the study, the follow-up period and treatments were not homogeneous. Third, TCZ itself may induce cytopenia[6] and might exacerbate the risk for cytopenia of MDS associated with VEXAS syndrome. Finally, the mechanism by which *UBA1* variants induce organ inflammation is not fully understood, and it is not clear whether IL-6 inhibition can suppress all the pathologies underlying VEXAS syndrome. In fact, a previous report showed only a transient benefit of TCZ in four patients, with a median duration of 8 months.[3] It took 30 months to diagnose VEXAS syndrome in RP16, which may be related to the accumulation of *UBA1* mutant cells and failure of TCZ treatment, implying the importance of early diagnosis. While not currently approved in Japan, stem cell transplantation may need to be considered for patients who have not responded to TCZ.[3 5] Although the data presented here demonstrate promise of TCZ in controlling symptoms associated with VEXAS syndrome, further case series, careful long-term observation and definition of primary endpoints are needed to optimise the treatment of VEXAS syndrome.

Yohei Kirino ,[1] **Kaoru Takase-Minegishi,**[1] **Naomi Tsuchida,**[1,2,3] **Lisa Hirahara,**[1] **Yosuke Kunishita** ,[1,4] **Ryusuke Yoshimi,**[1] **Hideaki Nakajima**[1]

[1]Department of Stem Cell and Immune Regulation, Yokohama City University Graduate School of Medicine, Yokohama, Kanagawa, Japan
[2]Department of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama, Kanagawa, Japan
[3]Department of Rare Disease Genomics, Yokohama City University Hospital, Yokohama, Kanagawa, Japan
[4]Department of Rheumatology, Yokohama Minami Kyosai Hospital, Yokohama, Kanagawa, Japan

Correspondence to Dr Yohei Kirino, Department of Stem Cell and Immune Regulation, Yokohama City University Graduate School of Medicine, Yokohama, Kanagawa 236-0004, Japan; kirino@yokohama-cu.ac.jp

Handling editor. Josef S Smolen

Acknowledgements The authors thank J. Ludovic Croxford, PhD, from Edanz Group (https://en-author-services.edanz.com/ac) for editing a draft of this manuscript.

Contributors Conception and design: YohK. Analysis and interpretation of the data, critical revision for important intellectual content and final approval of the article: all authors. Obtaining of funding: YohK, NT, YosK, RY and HN. Collection and assembly: YohK.

Funding This report was supported by grants from the Japanese Society for the Promotion of Science (JSPS) Grants-in-Aid for Scientific Research JP19H03700 (to YohK), JP20K17428 (to NT), JP19K23847 and JP20K17446 (to YosK), JP19K08914 (to RY), JP20H03714 (to HN), JP16H06277 (to CoBiA).

Competing interests YohK reports personal fees from Amgen and grants from Chugai and Ono, outside the submitted work. No other authors report competing interests.

Patient consent for publication Not required.

Ethics approval The study was approved by the Institutional Review Board in Yokohama City University School of Medicine (A121129002, A110124011).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220876).

To cite Kirino Y, Takase-Minegishi K, Tsuchida N, *et al*. *Ann Rheum Dis* 2021;**80**:1501–1502.

Received 28 May 2021
Accepted 9 June 2021
Published Online First 21 June 2021

Ann Rheum Dis 2021;**80**:1501–1502. doi:10.1136/annrheumdis-2021-220876

ORCID iDs
Yohei Kirino http://orcid.org/0000-0002-9488-661X
Yosuke Kunishita http://orcid.org/0000-0002-3915-9276

REFERENCES

1 Beck DB, Ferrada MA, Sikora KA, *et al*. Somatic mutations in *UBA1* and severe adult-onset autoinflammatory disease. *N Engl J Med* 2020;383:2628–38.
2 Tsuchida N, Kunishita Y, Uchiyama Y, *et al*. Pathogenic *UBA1* variants associated with VEXAS syndrome in Japanese patients with relapsing polychondritis. *Ann Rheum Dis* 2021;80:1057–61.
3 Bourbon E, Heiblig M, Gerfaud-Valentin M, *et al*. Therapeutic options in Vexas syndrome: insights from a retrospective series. *Blood* 2021. doi:10.1182/blood.2020010177. [Epub ahead of print: 22 Feb 2021].
4 Ferrada MA, Sikora KA, Luo Y, *et al*. Somatic mutations in UBA1 define a distinct subset of relapsing polychondritis patients with VEXAS syndrome. *Arthritis Rheumatol* 2021. doi:10.1002/art.41743. [Epub ahead of print: 28 Mar 2021].
5 van der Made CI, Potjewijd J, Hoogstins A, *et al*. Adult-Onset autoinflammation caused by somatic mutations in UBA1: a Dutch case series of VEXAS patients. *J Allergy Clin Immunol* 2021. doi:10.1016/j.jaci.2021.05.014. [Epub ahead of print: 25 May 2021].
6 Navarro-Millán I, Singh JA, Curtis JR. Systematic review of tocilizumab for rheumatoid arthritis: a new biologic agent targeting the interleukin-6 receptor. *Clin Ther* 2012;34:788–802.

Comment on 'Sustained discontinuation of infliximab with a raising-dose strategy after obtaining remission in patients with rheumatoid arthritis: the RRRR study, a randomised controlled trial' by Tanaka *et al*

We have read with interest the paper of Tanaka *et al*[1] and support the need for a more personalised approach in dosing regimens of tumour necrosis factor (TNF) inhibitors.[2] They adjusted infliximab dose based on TNF concentrations at baseline, under the assumptions that baseline TNF concentrations can be accurately measured, and that high disease activity (ie, more inflammation) is associated with higher TNF concentrations. However, several factors argue against these assumptions, which we would like to add to the study by Tanaka *et al*. These factors might explain the absence of an association between TNF concentrations and treatment response.

First, the quantification of TNF at baseline is in fact challenging: TNF is an unstable molecule with a short half-life.[3] Baseline concentrations in circulation are very low, around the detection limit of most immunoassays, even during active disease. It is doubtful that baseline TNF concentrations can be measured with sufficient accuracy and precision to serve as basis for individualised treatment decisions including the adjustment of infliximab dose.

Second, they suggested that low infliximab trough levels in non-responding patients might be a consequence of excessive TNF production and resultant high TNF plasma concentrations. However, we have recently been able to quantify total circulating TNF during adalimumab and etanercept treatment in rheumatoid arthritis patients.[4 5] On treatment, we observed an increase in circulating drug-bound TNF, reaching steady-state concentrations around 100–1000 pg/mL. This increase could be explained by a prolonged TNF half-life, due to its tight binding to the TNF inhibitor, which itself has a very long half-life. Nevertheless, steady-state TNF concentrations are still orders of magnitude lower than typical TNF inhibitor trough levels, also for infliximab. No association between TNF captured in circulation and concentrations of adalimumab and etanercept >1 µg/mL was observed.[4 5] It is therefore unlikely that TNF induces target-mediated clearance of infliximab, explaining the lower infliximab concentrations in patients with high baseline TNF. Instead, we suppose that low infliximab concentrations are mainly the result of antidrug antibody (ADA) formation.[6] Unfortunately, the association between serum drug concentration and ADA formation has not been addressed in the paper of Tanaka *et al*.

Finally, our recent data indicate that TNF concentrations in circulation are not at all reflective of (underlying) inflammation or disease activity, since steady-state TNF concentrations remained extremely stable for a follow-up of 2 years, irrespective of disease activity. Furthermore, to our surprise, we found a similar increase in circulating TNF in healthy volunteers who received a single dose of an adalimumab biosimilar.[4] This suggests that the majority of TNF in circulation most likely does not originate from pathological processes.

The aim of the study by Tanaka *et al* to personalise treatment is of significant value. Our recent results give an explanation why circulating TNF might not be an appropriate biomarker for treatment response, like Tanaka *et al* showed. Instead, the use of therapeutic drug monitoring to optimise the dose in clinical practice is of growing interest and could significantly contribute to personalised treatment.[2]

Lea C Berkhout ,[1] **Merel J l'Ami** ,[2] **Gerrit Jan Wolbink**,[1,2] **Theo Rispens** [1]

[1]Immunopathology, Sanquin Research, Amsterdam, The Netherlands
[2]Reade, Amsterdam Rheumatology and immunology Center, Amsterdam, The Netherlands

Correspondence to Dr Theo Rispens, Immunopathology, Sanquin Research, Amsterdam, The Netherlands; t.rispens@sanquin.nl

Contributors LCB, MJIA, GJW and TR have all made substantial contributions to the conception, drafting and revising of the work. All authors approved the final version.

Funding This study was funded by ZonMw, 2Treat (Grant 436001001).

Competing interests GJW has received a research grant from Pfizer (paid to the institution) and honoraria for lectures from UCB, Pfizer, AbbVie, Biogen and BMS. TR has received honoraria for lectures from Pfizer, AbbVie and Regeneron, and a research grant from Genmab.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

LCB and MJIA contributed equally.

To cite Berkhout LC, l'Ami MJ, Wolbink GJ, *et al*. *Ann Rheum Dis* 2021;**80**:e172.

Received 29 October 2019
Accepted 1 November 2019
Published Online First 19 November 2019

Linked

► http://dx.doi.org/10.1136/annrheumdis-2019-216593

Ann Rheum Dis 2021;**80**:e172. doi:10.1136/annrheumdis-2019-216557

ORCID iDs
Lea C Berkhout http://orcid.org/0000-0002-2282-1278
Merel J l'Ami http://orcid.org/0000-0001-9584-1088
Theo Rispens http://orcid.org/0000-0001-9600-1312

REFERENCES

1 Tanaka Y, Oba K, Koike T, *et al*. Sustained discontinuation of infliximab with a raising-dose strategy after obtaining remission in patients with rheumatoid arthritis: the RRRR study, a randomised controlled trial. *Ann Rheum Dis* 2020;79:94–102.
2 l'Ami MJ, Krieckaert CL, Nurmohamed MT, *et al*. Successful reduction of overexposure in patients with rheumatoid arthritis with high serum adalimumab concentrations: an open-label, non-inferiority, randomised clinical trial. *Ann Rheum Dis* 2018;77:484–7.
3 van der Poll T, van Deventer SJ, Hack CE, *et al*. Effects on leukocytes after injection of tumor necrosis factor into healthy humans. *Blood* 1992;79:693–8.
4 Berkhout LC, l'Ami MJ, Ruwaard J, *et al*. Dynamics of circulating TNF during adalimumab treatment using a drug-tolerant TNF assay. *Sci Transl Med* 2019;11:eaat3356.
5 Berkhout LC, l'Ami MJ, Krieckaert CLM, *et al*. The effect of methotrexate on tumour necrosis factor concentrations in etanercept-treated rheumatoid arthritis patients. *Rheumatology*. 2019. doi:10.1093/rheumatology/kez513. [Epub ahead of print: 06 Nov 2019].
6 Wolbink GJ, Vis M, Lems W, *et al*. Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;54:711–5.

Response to: 'Comment on 'Sustained discontinuation of infliximab with a raising-dose strategy after obtaining remission in patients with rheumatoid arthritis: the RRRR study, a randomised controlled trial' by Tanaka *et al*' by Berkhout *et al*

We would like to thank Berkhout *et al* for their comments on the absence of an association between serum TNF concentrations and treatment response to infliximab in our paper.[1]

First, reliability of the obtained results on the serum levels of TNF in the study should be firmly confirmed, because the quality control of the assessments was stringently managed by the laboratory company who assessed the serum.[2 3] However, as they mentioned, it remains unclear how serum levels of any cytokines reflect their tissue levels produced in inflamed tissues. There was a limitation in the context.

Second, serum levels of infliximab did not differ among the programmed treatment groups with low, intermediate and high levels of serum TNF at the baseline in the study, as shown in the online supplementary table 1.[2] Similar results were also seen in the RISING study.[4] However, because antidrug antibodies (ADA) were detected in some patients though very limited number, the assumption that low concentration of infliximab might be results of ADA formation cannot be excluded.

Third, we agree that serum levels of TNF may not adequately reflect inflammation and disease activity. The critical point of the study was that we could not escalate the dose until week 14 according to the approved usage by the government[2] and that it might reduce the efficacy of the programmed treatment strategy since the very start time may be the most important period to achieve a clinical remission by fine tuning the dose. However, recent progress in assessments of proteins using electrochemiluminescence and other methods would warrant improvement of the estimation of serum protein levels. Otherwise, are any surrogate markers better than TNF required for the treat-to-target instead of TNF itself?

Yoshiya Tanaka ,[1] **Koji Oba**,[2] **Tsutomu Takeuchi**[3]

[1]First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan
[2]Interfaculty Initiative in Information Studies, The University of Tokyo, Tokyo, Japan
[3]Rheumatology, Keio Univ, School of Medicine, Tokyo, Japan

Correspondence to Dr Yoshiya Tanaka, First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan; tanaka@med.uoeh-u.ac.jp

Handling editor Josef S Smolen

Contributors YT made the original manuscript, and KO and TT revised it.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2019-216593).

To cite Tanaka Y, Oba K, Takeuchi T. *Ann Rheum Dis* 2021;**80**:e173.

Received 2 December 2019
Accepted 2 December 2019
Published Online First 9 December 2019

► http://dx.doi.org/10.1136/annrheumdis-2019-216557

Ann Rheum Dis 2021;**80**:e173. doi:10.1136/annrheumdis-2019-216593

ORCID iD
Yoshiya Tanaka http://orcid.org/0000-0002-0807-7139

REFERENCES

1 Berkhout LC, l'Ami MJ, Wolbink GJ, *et al*. Comment on 'Sustained discontinuation of infliximab with a raising-dose strategy after obtaining remission in patients with rheumatoid arthritis: the RRRR study, a randomised controlled trial' by Tanaka *et al*. *Ann Rheum Dis* 2021;80:e172.
2 Tanaka Y, Oba K, Koike T, *et al*. Sustained discontinuation of infliximab with a raising-dose strategy after obtaining remission in patients with rheumatoid arthritis: the RRRR study, a randomised controlled trial. *Ann Rheum Dis* 2020;79:94–102.
3 Oba K, Horie N, Sato N, *et al*. Remission induction by raising the dose of remicade in RA (RRRR) study: rationale and study protocol for a randomized controlled trial comparing for sustained clinical remission after discontinuation of infliximab in patients with rheumatoid arthritis. *Contemp Clin Trials Commun* 2017;8:49–54.
4 Takeuchi T, Miyasaka N, Tatsuki Y, *et al*. Baseline tumour necrosis factor alpha levels predict the necessity for dose escalation of infliximab therapy in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;70:1208–15.

Gut-derived CD8$^+$ tissue-resident memory T cells are expanded in the peripheral blood and synovia of SpA patients

We read with interest the recently published paper from Qaiyum *et al*[1] demonstrating a novel integrin-expressing mature Crohn's disease (CD)8$^+$ T cell population defined as CD49a$^+$CD103$^+$β7$^+$CD29$^+$ cells in the synovial fluids of ankylosing spondylitis (AS) patients. Although the authors did not analyse gut samples from AS patients, they speculate that these cells might be gut-derived cells. Interestingly, as stated by authors, the transcriptional and phenotypic signature of these cells is reminiscent of human tissue-resident memory T cells (T_{RM}). T_{RM} are a subset of cells important as the first line of defence from infection in mucosal tissues, never studied in spondyloarthritis (SpA).[2] For clarifying whether these cells could be of intestinal original, we set up additional analyses, wondering if we could see similar results in paired samples of patients with SpA.

Paired gut and synovial samples and fluids and peripheral blood samples (PCMCs) were obtained from patients with SpA (HLA-B27 positive; n=6), never treated with biologic agents at the time of sample collection. Gut samples were also obtained from healthy controls (HCs) (HLA-B27 negative; n=6) and synovial tissues from osteoarthritis (OA) patients (HLA-B27 negative; n=6). Peripheral blood mononuclear cells (PBMCs) were also obtained from HCs. CD103 and CD8 expression were assessed by immunohistochemistry. The percentage of T_{RM} T cells (defined as CD8$^+$CD69$^+$CD103$^+$cells) among isolated lamina propria mononuclear cells (LPMCs) and PBMCs from SpA patients and controls were also analysed by flow cytometry.

Part of the results is shown in figure 1. In the gut tissues, the number of CD8$^+$CD103$^+$ cells was consistently increased in the inflammatory SpA samples compared with non-inflammatory samples (figure 1A–E). Tissue distribution confirmed their predominant localisation in the context of epithelial layer (figure 1A–D). Flow cytometric analysis of LPMCs confirmed the expansion of CD8$^+$CD69$^+$CD103$^+$ T_{RM} T cells, mainly

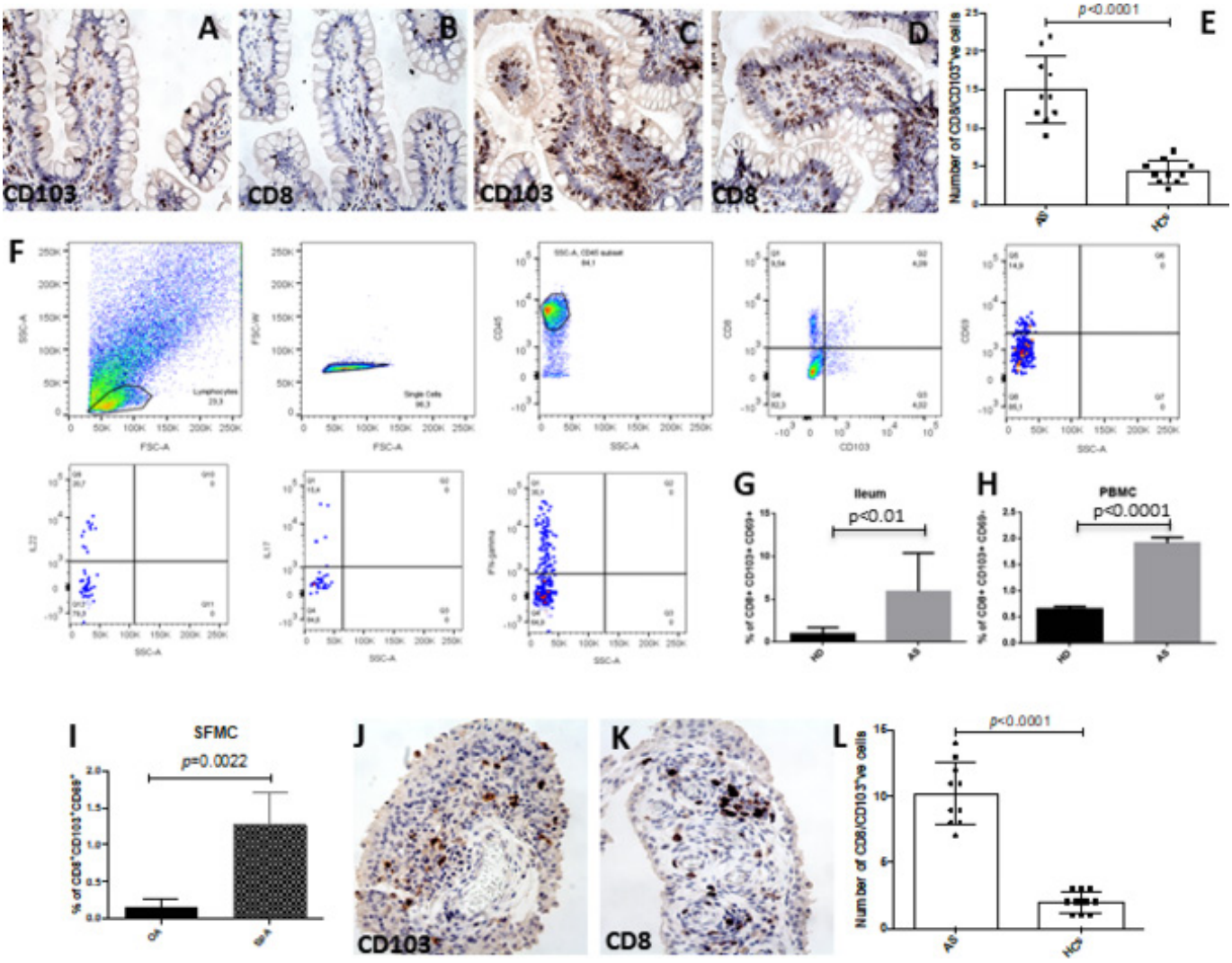


Figure 1 T_{RM}s in the gut, peripheral blood and synovia of SpA patients. (A–D) Representative imaging showing CD103 (A and C) and CD8 (B and D) expression in sequential gut sections of controls (A–B) and SpA patients (C–D). (E) Higher numbers of CD8/CD103 positive cells were observed in SpA patients compared with controls. (F) Representative dot plots showing gating strategy for T_{RM}s in the peripheral blood of SpA patients. (G–I) Percentages of T_{RM}s among LPMC (G), PBMC (H) and SFMC (I) in SpA patients and controls. (J–K) Representative imaging showing CD103 (J) and CD8 (K) expression in sequential synovial sections of SpA patients. (L) Higher numbers of CD8/CD103 positive cells were observed in SpA patients compared with controls. (A–D) and (J–K): Original magnification ×250. LPMC, lamina propria mononuclear cell; PBMC, peripheral blood mononuclear cell; T_{RM}s, tissue-resident memory T cells.

producing IFNγ, in SpA patients compared with HCs (figure 1F–G). The expansion of $CD8^+CD69^+CD103^+$ T_{RM} T cells, mainly producing IFNγ, was also confirmed in SpA PBMCs (figure 1H) and synovial mononuclear cells (SFMC) (figure 1I), compared with HCs. The majority of circulating and synovial fluids $CD8^+CD69^+CD103^+$ T_{RM} expressed the intestinal homing receptor α4β7 (67% and 75%, respectively) suggesting their gut origin (data not shown). Finally, immunohistochemical analysis of sequential synovial samples confirmed tissue infiltration of $CD8^+CD103^+$ cells in the inflamed synovial tissues of SpA patients (figure 1J–L).

The existence of a gut–joint has been hypothesised in SpA patients.[3] The inflamed gut could actively participate in the pathogenesis of SpA through the production of proinflammatory cytokines, such as IL-23p19[4] and IL-9,[5] and the differentiation of potentially pathogenic innate cells producing IL-22 and IL-17.[3] T_{RM} are a critical component of mucosal immune defence by acting as peripheral sentinels capable of rapidly mobilising protective tissue immunity on pathogen recognition.[2] Our data confirm the expansion of T_{RM} in the synovial compartment of SpA patients, providing evidence of T_{RM} expansion in the peripheral blood and the gut. The expression of α4β7 by circulating T_{RM} in SpA might support the re-circulation of these cells from the gut to the peripheral blood and inflamed joints.

Giuliana Guggino,[1] Aroldo Rizzo,[2] Daniele Mauro,[3] Federica Macaluso,[1] Francesco Ciccia [3]

[1]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, Università degli Studi di Palermo, Palermo, Italy
[2]Dipartimento di Oncologia, Azienda Ospedaliera Villa Sofia-Cervello, Palermo, Italy
[3]Dipartimento di Medicina di Precisione, Università degli Studi della Campania Luigi Vanvitelli, Napoli, Italy

Correspondence to Dr Francesco Ciccia, Dipartimento di Medicina di Precisione, Università degli Studi della Campania Luigi Vanvitelli, Napoli 80131, Italy; francescociccia@tiscali.it

Handling editor Josef S Smolen

Contributors All the authors gave substantial contributions to the conception or design of the work, the acquisition, analysis or interpretation of data, drafting the work or revising it critically for important intellectual content, or final approval of the version published. All the authors agree to 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.

Funding This study was in part supported by a grant of Ministero dell'Istruzione, dell'Università e della Ricerca Scientifica from Italy.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Guggino G, Rizzo A, Mauro D, *et al*. *Ann Rheum Dis* 2021;**80**:e174.

Received 10 October 2019
Accepted 13 October 2019
Published Online First 18 October 2019

Linked

► http://dx.doi.org/10.1136/annrheumdis-2019-216472

Ann Rheum Dis 2021;**80**:e174. doi:10.1136/annrheumdis-2019-216456

ORCID iD
Francesco Ciccia http://orcid.org/0000-0002-9352-1264

REFERENCES

1 Qaiyum Z, Gracey E, Yao Y, *et al*. Integrin and transcriptomic profiles identify a distinctive synovial CD8+ T cell subpopulation in spondyloarthritis. *Ann Rheum Dis* 2019;78:1566–75.
2 Schenkel JM, Masopust D. Tissue-Resident memory T cells. *Immunity* 2014;41:886–97.
3 Rizzo A, Ferrante A, Guggino G, *et al*. Gut inflammation in spondyloarthritis. *Best Pract Res Clin Rheumatol* 2017;31:863–76.
4 Ciccia F, Guggino G, Zeng M, *et al*. Proinflammatory CX3CR1+CD59+Tumor necrosis factor-like molecule 1A+Interleukin-23+ monocytes are expanded in patients with ankylosing spondylitis and modulate innate lymphoid cell 3 immune functions. *Arthritis Rheumatol* 2018;70:2003–13.
5 Ciccia F, Guggino G, Ferrante A, *et al*. Interleukin-9 overexpression and Th9 polarization characterize the inflamed gut, the synovial tissue, and the peripheral blood of patients with psoriatic arthritis. *Arthritis Rheumatol* 2016;68:1922–31.

Response to: 'Gut-derived CD8+ tissue-resident memory T cells are expanded in the peripheral blood and synovia of SpA patients' by Guggino *et al*

We were pleased to receive the correspondence of Guggino *et al*[1] commenting on our recent publication.[2] Their studies confirm our findings of an expansion of cells with an expression profile consistent with tissue-resident memory cells (TRMs) in synovial fluid of spondyloarthritis (SpA). They have added the valuable insight that these cells are also expanded in gut tissues of patients with SpA.

The CD8+ T cell in question reported by Guggino and colleagues, and the InEx cells in our paper, may well be TRMs. But at present, the field is wrestling with nomenclature. First, resident memory cells, by definition, do not leave the tissues in which they reside.[3] This tissue retention is best characterised by the expression of CD69, which blocks S1PR activity, hence limiting TRMs egress from tissue to the blood where S1P levels are high.[4] Second, as Guggino *et al* point out, many of the CD8+ T cells present in the gut are closely associated with the epithelia. CD8+ T cells in the gut epithelia are the prototypic intestinal epithelial lymphocyte (IEL), hence labelling the cells under discussion exclusively as TRMs should also acknowledge a large body of research on IEL. For example, CD8+ IEL were recently found to be depleted in gut biopsies from patients with HLA-B27+ axial SpA.[5]

The interplay of gut and joint inflammation has been supported by the clinical overlap between SpA and inflammatory bowel disease (IBD)[6] and between gut infection and reactive arthritis[7] as well as shared genetic susceptibility between IBD and ankylosing spondylitis.[6] Cells that posses a gut-resident phenotype that are expanded in the SpA joint include TRM and mucosa-associated invariant T cells,[8] the latter contributing to the interleukin 17-mediated inflammation in axial spondyloarthritis. Therapeutic modulation of gut–joint trafficking holds the potential for novel treatment approaches to SpA.

Zoya Qaiyum ,[1] **Eric Gracey**,[2] **YuChen Yao**,[3] **Robert D Inman**[1,4]

[1]Krembiil Research Institute, Toronto, Ontario, Canada
[2]Rheumatology, University of Ghent, Gent, Belgium
[3]Toronto, Ontario, Canada
[4]Spondylitis Program, University Health Network, Toronto, Ontario, Canada

Correspondence to Dr Robert D Inman, Spondylitis Program, University Health Network, Toronto, Ontario, Canada; robert.inman@uhn.ca

Handling editor Josef S Smolen

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Qaiyum Z, Gracey E, Yao YC, *et al*. *Ann Rheum Dis* 2021;**80**:e175.

Received 19 November 2019
Revised 9 December 2019
Accepted 9 December 2019
Published Online First 18 December 2019

Linked

► http://dx.doi.org/10.1136/annrheumdis-2019-216456

Ann Rheum Dis 2021;**80**:e175. doi:10.1136/annrheumdis-2019-216472

ORCID iD
Zoya Qaiyum http://orcid.org/0000-0002-1698-0360

REFERENCES

1 Guggino G, Rizzo A, Mauro D, *et al*. Gut-derived CD8 $^{+}$ tissue-resident memory T cells are expanded in the peripheral blood and synovia of SpA patients. *Ann Rheum Dis* 2021;80:e174.
2 Qaiyum Z, Gracey E, Yao Y, *et al*. Integrin and transcriptomic profiles identify a distinctive synovial CD8+ T cell subpopulation in spondyloarthritis. *Ann Rheum Dis* 2019;78:1566–75.
3 Masopust D, Soerens AG. Tissue-Resident T cells and other resident leukocytes. *Annu Rev Immunol* 2019;37:521–46.
4 Mackay LK, Braun A, Macleod BL, *et al*. Cutting edge: CD69 interference with sphingosine-1-phosphate receptor function regulates peripheral T cell retention. *J.i.* 2015;194:2059–63.
5 Regner EH, Ohri N, Stahly A, *et al*. Functional intraepithelial lymphocyte changes in inflammatory bowel disease and spondyloarthritis have disease specific correlations with intestinal microbiota. *Arthritis Res Ther* 2018;20.
6 Chan J, Sari I, Salonen D, *et al*. Prevalence of sacroiliitis in inflammatory bowel disease using a standardized computed tomography scoring system. *Arthritis Care Res* 2018;70:807–10.
7 Gracey E, Dumas E, Yerushalmi M, *et al*. The ties that bind: skin, gut and spondyloarthritis. *Curr Opin Rheumatol* 2019;31:62–9.
8 Gracey E, Qaiyum Z, Almaghlouth I, *et al*. Il-7 primes IL-17 in mucosal-associated invariant T (MAIT) cells, which contribute to the Th17-axis in ankylosing spondylitis. *Ann Rheum Dis* 2016;75:2124–32.

Gut microbiome in rheumatic diseases

In a recent study, Deshayes *et al* used 16S ribosomal RNA gene sequencing to analyse the gut microbiome in patients with familial Mediterranean fever (FMF) complicated or not by AA amyloidosis and in patients with AA amyloidosis of another origin.[1] Compared with healthy controls, FMF was associated with decreased α-diversity (ie, microbial richness and evenness) and altered composition of the gut microbiome. Certain operational taxonomy units (OTUs) belonging to the *Clostridiales* were associated with FMF, whereas two OTUs were overrepresented in AA amyloidosis among FMF patients. The authors suggested that intestinal microorganisms may play a role in the clinical expression and pathogenesis of these diseases. In a similar study, decreased species richness diversity was shown in the microbiome of patients with systemic lupus erythematosus (SLE). Moreover, SLE was associated with intestinal outgrowth of *Ruminococcus gnavus* of the *Lachnospiraceae* family that was most pronounced in those with lupus nephritis and correlated with disease activity.[2]

These and previous studies in spondyloarthritis and rheumatoid arthritis reflect the growing interest of researchers to the role of the gut microbiome in shaping local and systemic immune responses and in pathogenesis of various rheumatic diseases.[3] We agree with Deshayes *et al* that in the future microbiome engineering might be a useful approach to control FMF and other rheumatic diseases, for example, via correction of the altered signalling pathways, production of metabolites with drug-like activities or anti-inflammatory molecules.[4] The utility of this strategy will probably depend on the specific role of the microbiome in the complex interplay of genetics, environment and immunity at different stages of a particular disease. Targeting each of these key components might be necessary to restore the equilibrium between them.[3]

However, the clinical significance of the currently available evidence should not be overestimated, and it is too early to make any far-reaching conclusions. Which came first: the chicken or the egg? This causality dilemma always arises during microbiome studies revealing associations with health or disease.[5] The old adage that 'correlation does not imply causation' was recently reinforced by Duvallet *et al* who performed a cross-disease meta-analysis of 28 published case-control gut microbiome studies.[6] Some diseases were characterised by the presence of potentially pathogenic bacteria, while others showed a depletion of health-associated microbes. Nevertheless, many bacteria, which related to certain diseases in individual studies, in fact, were non-specifically associated with multiple disorders, indicating a shared response to health and disease.

Gut microbiome composition differs across regions and ethnicities, changes over time, and can be influenced by multiple factors, including, among others, diet, lifestyle, hormonal cycles, disease, comorbidity, exposure to antimicrobial agents, and so on. Certain region-specific factors influencing gut microbiome composition could predominate over others, which may have a profound impact on the results of the screening studies. In the Dutch population, individuals belonging to a certain ethnic group and living in the same city tended to share gut microbiota characteristics. Hence, the ethnic origin of individuals may be an important factor to consider in microbiome research,[7] particularly in patients with FMF, which shows a marked ethnic distribution.

Antibiotic and non-antibiotic drug use may be another confounding factor in gut microbiome studies. Maier *et al* found that 24% of more than 1000 drugs, including members of all therapeutic classes, inhibited the growth of at least one representative gut bacterial strain.[8] Of note, side effects resembling those of antibiotics, for example, diarrhoea, which frequently occurs in colchicine users, were associated with anticommensal activity. Therefore, regular drug treatment may contribute to a decrease in the diversity of microbiomes.

Proof-of-concept studies using disease-associated bacteria are needed to establish the implication of putative candidate for the onset of disease or its beneficial effects.[5] Such research will be a challenge for investigators since many gut bacteria are present in low numbers and cannot be cultivated in quantities sufficient for in vivo testing.[9] Moreover, the choice of microbiota subpopulation, that is, faecal, luminal or mucosa-associated, might be important for a proper stratification of patients.[5]

In summary, it is well-known that pathogenic microorganisms contribute to the aetiology and/or clinical course of certain rheumatic diseases, that is, reactive arthritis (genitourinary or gastrointestinal infections), polyarteritis nodosa (hepatitis B virus (HBV)), cryoglobulinaemic vasculitis (hepatitis C virus (HCV)) or granulomatosis with polyangiitis (*Staphylococcus aureus*). Vaccination against HBV infection has already resulted in a significant decrease in the incidence of polyarteritis nodosa, whereas wider treatment coverage of patients with HCV infection may have a similar effect on the epidemiology of HCV-associated cryoglobulinaemic vasculitis.[10] Pioneering research of human microbiome is likely to provide greater insights into the mechanisms of inflammatory disease and may even lead to new treatment or prevention solutions. However, disease associations from the individual case-control studies should be interpreted with caution since most of them may found to be non-specific and indicative of a shared response to disease.[6] *Correlation isn't causation, but sure is a hint* (Edward Tufte, American Statistician).

Sergey Moiseev , Vilen Rameev, Ekaterina Karovaikina, Lidia Lysenko (Kozlovskaya)

Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russian Federation

Correspondence to Professor Sergey Moiseev, Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow 119435, Russian Federation; avt420034@yahoo.com

Handling editor Josef S Smolen

Contributors All the authors participated in the preparation of the manuscript.

Funding The study is funded by the Russian Academic Excellence Project 5-100.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Moiseev S, Rameev V, Karovaikina E, *et al*. *Ann Rheum Dis* 2021;**80**:e176.

Received 29 October 2019
Accepted 1 November 2019
Published Online First 14 November 2019

Ann Rheum Dis 2021;**80**:e176. doi:10.1136/annrheumdis-2019-216560

ORCID iD
Sergey Moiseev http://orcid.org/0000-0002-7232-4640

REFERENCES

1 Deshayes S, Fellahi S, Bastard J-P, *et al*. Specific changes in faecal microbiota are associated with familial Mediterranean fever. *Ann Rheum Dis* 2019;78:1398–404.
2 Azzouz D, Omarbekova A, Heguy A, *et al*. Lupus nephritis is linked to disease-activity associated expansions and immunity to a gut commensal. *Ann Rheum Dis* 2019;78:947–56.
3 Van de Wiele T, Van Praet JT, Marzorati M, *et al*. How the microbiota shapes rheumatic diseases. *Nat Rev Rheumatol* 2016;12:398–411.
4 Balakrishnan B, Taneja V. Microbial modulation of the gut microbiome for treating autoimmune diseases. *Expert Rev Gastroenterol Hepatol* 2018;12:985–96.
5 Lynch SV, SC N, Shanahan F, *et al*. Translating the gut microbiome: ready for the clinic? *Nat Rev Gastroenterol Hepatol* 2019.
6 Duvallet C, Gibbons SM, Gurry T, *et al*. Meta-Analysis of gut microbiome studies identifies disease-specific and shared responses. *Nat Commun* 1784;2017.
7 Deschasaux M, Bouter KE, Prodan A, *et al*. Depicting the composition of gut microbiota in a population with varied ethnic origins but shared geography. *Nat Med* 2018;24:1526–31.
8 Maier L, Pruteanu M, Kuhn M, *et al*. Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature* 2018;555:623–8.
9 Browne HP, Forster SC, Anonye BO, *et al*. Culturing of 'unculturable' human microbiota reveals novel taxa and extensive sporulation. *Nature* 2016;533:543–6.
10 Moiseev S, Novikov P, Mukhin N. Hcv-Associated cryoglobulinemia vasculitis: are its days numbered? *Ann Rheum Dis* 2017;76:e5.

The level of peripheral regulatory T cells is linked to changes in gut commensal microflora in patients with systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder mainly mediated by lymphocytes and autoantibodies, which have a pervasive negative impact on the majority of organs.[1 2] It deserves more attention to further explore the pathogenesis because of the unclear complex pathogenesis and the limited clinical efficacy of SLE treatment.

Recently, a cross-sectional discovery cohort in the USA conducted by Azzouz *et al,* published in *Annals of Rheumatic Diseases,* suggested that specific gut commensal strains, especially *Ruminococcus gnavus*, may contribute to the disease activity and autoantibody production in SLE patients,[3] which put forward a novel concept for the immune pathogenesis of SLE. Their study was well performed and analysed the abundance of intestinal flora and sera profiled for antibacterial and autoantibody responses between SLE patients with the different disease activity index scores and matched healthy controls. However, the faecal microbiota is lacking a precise link with lymphocytes in peripheral blood of the patients, which are the important participants of immune mechanism of SLE.

In this study, we studied the correlation between the changes in faecal microbial diversity and the absolute numbers of peripheral lymphocyte subgroups and CD4+ T subsets in SLE patients, especially regulatory T cells (Tregs) that mediate immune tolerance and maintain immunological homeostasis.[4] The blood and stool samples were collected from 92 patients with SLE and 217 matched healthy adults. The 16S rRNA in the stool specimens were sequenced using the Roche/45 high-throughput sequencing platform. The absolute numbers of circulating lymphocytes and CD4+ T subgroups of these individuals were detected by flow cytometry combined with standard absolute counting beads.[5]

Patients with SLE, regardless male or female, had different taxonomic diversity and abundance of specific strains of a gut commensal at the level of the phylum, family and genus ($p<0.05$) from healthy controls. They had higher levels of Proteobacteria, Bacteroidetes and Actinobacteria and a lower level of Firmicutes as compared with those of healthy controls at the phylum level ($p<0.05$). In addition, at the family or genus level, the proportion or abundance of gut bacteria in SLE patients, including Bacteroidaceae, Veillonellaceae, *Klebsiella*, Streptococcaceae and Erysipelotrichaceae, differed from those in healthy individuals with statistically significant difference ($p<0.05$) (table 1). It was noteworthy that patients with SLE had significantly lower proportion of Ruminococcaceae at family level than healthy controls ($p<0.001$). Interestingly, the percentage of *Ruminococcus* at genus level was higher in SLE patients ($p<0.05$), which was confirmed to involved in the incidence of lupus in Azzouz *et al*'s study, suggesting that we should study the related bacterial flora and its mechanism of SLE patients at multiple levels.

We found that the proportion of *Ruminococcus* was correlated with the absolute counts of lymphocytes, suggesting that the changed of intestinal flora was involved in the imbalance of proinflammation and anti-inflammation T cells in SLE. Particularly, the proportion of *Ruminococcus* was significantly correlated with the absolute counts of Tregs (its dysfunction was one of the crucial immune mechanisms in the onset of lupus)[6] and the ratio of Th1/Th2 and Th17/Treg (figure 1D–F), but not with the numbers of Th1, Th2 and Th17 cells (figure 1A–C), which may be one of the reasons for the changes in intestinal microbial population are involved in SLE patients. However, there was no obvious correlation between the abundance of *Ruminococcus* and the absolute numbers of total T, B, natural killer (NK), CD4+ T and CD8+ T cells ($p>0.05$).

Table 1 Shifts in taxonomic abundance between SLE and healthy controls (HC) (mean±SD)

Taxonomy	SLE (%)	HC (%)	P value
Phylum			
Proteobacteria	13.26±21.77	2.65±3.56	<0.001
Firmicutes	40.14±25.58	59.20±19.19	<0.001
Bacteroidetes	42.69±25.26	35.75±18.58	0.018
Actinobacteria	2.25±3.49	1.26±3.28	0.002
Family			
Lachnospiraceae	16.35±13.09	25.09±12.89	<0.001
Ruminococcaceae	12.72±12.68	23.50±13.57	<0.001
Bacteroidaceae	35.12±25.56	26.67±18.03	0.021
Veillonellaceae	2.63±5.42	5.68±9.30	<0.001
Streptococcaceae	1.26±5.56	0.24±1.49	<0.001
Genus			
Ruminococcus	2.63±6.59	1.41±2.04	0.016
Haemophilus	0.15±0.53	0.17±0.59	0.035
Faecalibacterium	7.58±9.80	19.99±13.87	<0.001
Bacteroides	38.75±26.96	30.61±19.8	0.016
Clostridium IV	0.17±0.40	0.27±0.51	<0.001
Klebsiella	3.04±9.39	0.30±1.54	0.001
Erysipelotrichaceae	0.06±0.32	0.02±0.13	<0.001

SLE, systemic lupus erythematosus.

In conclusion, the changes in taxonomic diversity and the abundance of partial specific flora, such as *Ruminococcus* genus, may regulate the absolute number of Tregs in peripheral blood to participate in the pathogenesis of SLE. This study on the correlation between the intestinal flora abundance and levels

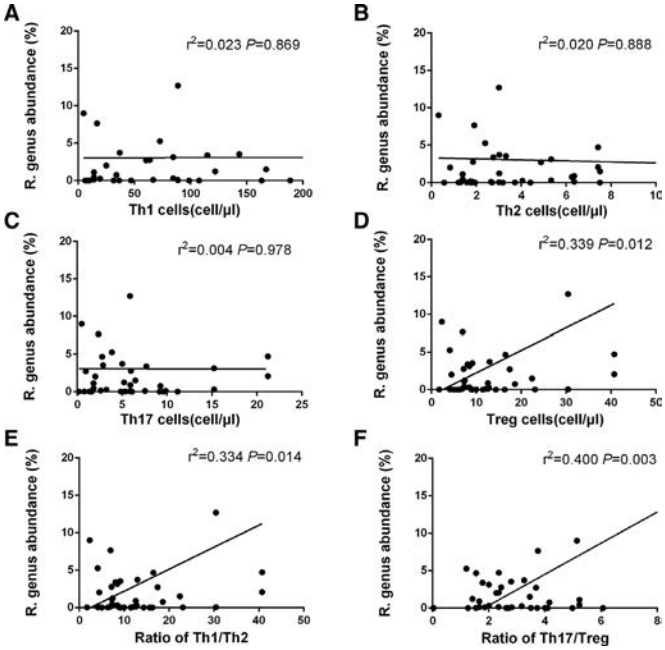


Figure 1 Correlation of absolute numbers of CD4+ T subsets and the ratio of Th1/Th2 and Th17/Treg with the propotion of *Ruminococcus* at genus level in SLE patients by Spearman coefficient. All p values reported herein are two-tailed. P<0.05 was taken as statistical significance. SLE, systemic lupus erythematosus.

of lymphocyte subsets reconfirmed the involvement of gut commensal microflora in the pathogenesis of SLE.

Sheng-Xiao Zhang ,[1,2] **Jia Wang**,[1,2] **Jun-Wei Chen**,[2] **Ming-Xing Zhang**,[2] **Yi-Fan Zhang**,[3] **Fang-Yuan Hu**,[2] **Zhi-Qin Lv**,[2] **Chong Gao**,[4] **Ya-Feng Li**,[5] **Xiao-Feng Li**[1,2]

[1]Department of Rheumatology, Shanxi Li Xiaofeng Medical Groups, Taiyuan, China
[2]Department of Rheumatology, The Second Hospital of Shanxi Medical University, Taiyuan, China
[3]Department of Clinical Medicine, Shanxi Medical University, Taiyuan, China
[4]Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[5]Department of Nephrology, Precision Medicine Center, The Shanxi Provincial People's Hospital, Shanxi Medical University, Taiyuan, China

Correspondence to Professor Xiao-Feng Li; lxf_9859@sxmu.edu.cnDr Ya-Feng Li; Dr.yafengli@gmail.com

Contributors Study design and manuscript writing: S-XZ and JW. Data extraction, quality assessment, analysis and interpretation of data: S-XZ, JW and JC. 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. Y-FL and XL 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.

Funding This work was supported by a grant from the National Natural Science Foundation of China (81871295).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

S-XZ and JW contributed equally.

To cite Zhang S-X, Wang J, Chen J-W, *et al*. *Ann Rheum Dis* 2021;**80**:e177.

Received 20 October 2019
Accepted 22 October 2019
Published Online First 15 November 2019

Linked

► http://dx.doi.org/10.1136/annrheumdis-2019-216523

Ann Rheum Dis 2021;**80**:e177. doi:10.1136/annrheumdis-2019-216504

ORCID iD
Sheng-Xiao Zhang http://orcid.org/0000-0003-1341-7588

REFERENCES

1 Vasquez-Canizares N, Wahezi D, Putterman C. Diagnostic and prognostic tests in systemic lupus erythematosus. *Best Pract Res Clin Rheumatol* 2017;31:351–63.
2 Mohan C, Putterman C. Genetics and pathogenesis of systemic lupus erythematosus and lupus nephritis. *Nat Rev Nephrol* 2015;11:329–41.
3 Azzouz D, Omarbekova A, Heguy A, *et al*. Lupus nephritis is linked to disease-activity associated expansions and immunity to a gut commensal. *Ann Rheum Dis* 2019;78:947–56.
4 He J, Zhang X, Wei Y, *et al*. Low-dose interleukin-2 treatment selectively modulates CD4(+) T cell subsets in patients with systemic lupus erythematosus. *Nat Med* 2016;22:991–3.
5 Miao M, Hao Z, Guo Y, *et al*. Short-Term and low-dose IL-2 therapy restores the Th17/Treg balance in the peripheral blood of patients with primary Sjögren's syndrome. *Ann Rheum Dis* 2018;77:1838–40.
6 Zhang S-X, Ma X-W, Li Y-F, *et al*. The proportion of regulatory T cells in patients with systemic lupus erythematosus: a meta-analysis. *J Immunol Res* 2018;2018:1–11.

Response to: 'The level of peripheral regulatory T cells is linked to changes in gut commensal microflora in patients with systemic lupus erythematosus' by Zhang *et al* and the phylogeny of a candidate pathobiont in lupus nephritis

We appreciate the opportunity to respond to the correspondence from Zhang *et al*,[1] and fully agree with the importance of elucidating the specific roles of individual taxa in clinical lupus pathogenesis. These authors assert that the candidate pathobiont in our earlier paper 'is lacking in a precise link with lymphocytes…'. Yet, this is completely erroneous as we showed that lupus patients with expansions of the *Ruminococcus gnavus* species also had circulating antibodies that recognised strain-restricted lipoglycan antigens in this candidate pathobiont species.[2] These peripheral immune responses were also shown to be cross-reactive with IgG anti-native DNA antibodies that have well-documented roles in lupus pathogenesis. Of course, circulating antibodies are produced by peripheral B cells and end-differentiated plasma cells. Indeed, the importance of this type of mechanistic link has also been demonstrated in mice colonised with the commensal Akkermansia species, which has some potential properties akin to our candidate pathobiont, and also has mucinolytic properties that may contribute to gut leakiness and can similarly induce systemic species-specific systemic IgG responses.[3]

Zhang *et al* seek to highlight their own observations regarding a direct correlation between the level of T cells in the blood, bearing a Treg phenotype, and gut abundance of the *Ruminococcus* genus, based on 16S rRNA library analysis. Direct evidence, however, of immune recognition of antigens from this taxa by peripheral Tregs is missing.

Notably, there appears to be a serious misunderstanding on the part of these authors. As stated in our paper, *R. gnavus* was originally mis-assigned within bacterial phylogeny and in fact it is neither a member of the genus *Ruminococcus* nor the family Ruminococcaceae, but is in the genus Blautia in the family Lachnospiraceae.[4 5] Hence the analysis presented of their lupus cohort database of phylogenetic representation is not directly relevant to our findings. These names are unfortunately confusing, although the correct phylogenetic assignments have been sorted out.[4 5]

Our report further explained the greater potential implications of host colonisation by *R. gnavus*[2] and this species has now been implicated in several inflammatory and autoimmune diseases (discussed by Silverman *et al*[6]). Moreover, the link between *R. gnavus* with lupus, a disease with a strong hallmark of B-cell abnormalities and autoantibody production, may be intimately intertwined with the local production and postulated systemic release of a recently identified *R. gnavus* outer membrane protein with the properties of a B-cell superantigen.[7] Taken together, these findings highlight the limits of 16S rRNA based taxa assignments as greater mechanistic insights will in part require the characterisation of *R. gnavus* strains from lupus patients with active disease.

Gregg J Silverman , **Doua F Azzouz**

Department of Medicine, New York University School of Medicine, New York, New York, USA

Correspondence to Dr Gregg J Silverman, New York University School of Medicine, New York, NY 10016, USA; gregg.silverman@nyumc.org

Handling editor Josef S Smolen

Contributors GJS and DA contributed to the formulation and writing of this response.

Funding Supported in part by P50AR070591-01A1, 1R01AI143313-01 and the Colton Foundation.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Silverman GJ, Azzouz DF. *Ann Rheum Dis* 2021;**80**:e178.

Received 31 October 2019
Accepted 1 November 2019
Published Online First 15 November 2019

Linked

► http://dx.doi.org/10.1136/annrheumdis-2019-216504

Ann Rheum Dis 2021;**80**:e178. doi:10.1136/annrheumdis-2019-216523

ORCID iD
Gregg J Silverman http://orcid.org/0000-0001-9480-9457

REFERENCES

1 Zhang S-X, Wang J, Chen J, *et al*. The level of peripheral regulatory T cells is linked to changes in gut commensal microflora in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2021;80:e177.
2 Azzouz D, Omarbekova A, Heguy A, *et al*. Lupus nephritis is linked to disease-activity associated expansions and immunity to a gut commensal. *Ann Rheum Dis* 2019;78:947–56.
3 Ansaldo E, Slayden LC, Ching KL, *et al*. *Akkermansia muciniphila* induces intestinal adaptive immune responses during homeostasis. *Science* 2019;364:1179–84.
4 Liu C, Finegold SM, Song Y, *et al*. Reclassification of Clostridium coccoides, Ruminococcus hansenii, Ruminococcus hydrogenotrophicus, Ruminococcus luti, Ruminococcus productus and Ruminococcus schinkii as Blautia coccoides gen. nov., comb. nov., Blautia hansenii comb. nov., Blautia hydrogenotrophica comb. nov., Blautia luti comb. nov., Blautia producta comb. nov., Blautia schinkii comb. nov. and description of Blautia wexlerae sp. nov., isolated from human faeces. *Int J Syst Evol Microbiol* 2008;58:1896–902.
5 Togo AH, Diop A, Bittar F, *et al*. Description of Mediterraneibacter massiliensis, gen. nov., sp. nov., a new genus isolated from the gut microbiota of an obese patient and reclassification of Ruminococcus faecis, Ruminococcus lactaris, Ruminococcus torques, Ruminococcus gnavus and Clostridium glycyrrhizinilyticum as Mediterraneibacter faecis comb. nov., Mediterraneibacter lactaris comb. nov., Mediterraneibacter torques comb. nov., Mediterraneibacter gnavus comb. nov. and Mediterraneibacter glycyrrhizinilyticus comb. nov. *Antonie Van Leeuwenhoek* 2018;111:2107–28.
6 Silverman GJ, Azzouz DF, Alekseyenko AV. Systemic lupus erythematosus and dysbiosis in the microbiome: cause or effect or both? *Curr Opin Immunol* 2019;61:80–5.
7 Bunker JJ, Drees C, Watson AR, *et al*. B cell superantigens in the human intestinal microbiota. *Sci Transl Med* 2019;11. doi:10.1126/scitranslmed.aau9356. [Epub ahead of print: 28 Aug 2019].

Bone health in patients with systemic lupus erythematosus

The association between systemic lupus erythematosus and other comorbidities has been extensively studied.[1 2] Recently, an article written by Orsolini *et al* published in *Annals of the Rheumatic Diseases* commented that osteoporosis and fractures are frequently found in patients with systemic lupus erythematosus.[3] Orsolini *et al*'s article is a timely one and provides the updated concepts to the readers. Some points are discussed here. A cohort study in South Korea conducted by Kim *et al* reported that the incidence of fractures was higher in patients with systemic lupus erythematosus than those with non-lupus (19 vs 6.5 per 1000 person-years).[4] A cohort study in USA conducted by Tedeschi *et al* reported that the incidence of fractures was higher in the systemic lupus erythematosus group than comparison group (4.32 vs 2.4 per 1000 person-years).[5] Both studies further confirm that patients with systemic lupus erythematosus are substantially at increased risk of fractures.

In order to support the Orsolini *et al*'s comments and to test the association between systemic lupus erythematosus and major osteoporotic fractures, a preliminary cohort study was performed using the 2005–2012 database of the Taiwan National Health Insurance Program with 23 million persons living in Taiwan.[6 7] At the baseline, patients ≥40 years with a new diagnosis of systemic lupus erythematosus were selected as the systemic lupus erythematosus group. Patients ≥40 years without a diagnosis of systemic lupus erythematosus were identified as the non-lupus group. The main outcome was a new diagnosis of any major osteoporotic fractures including fractures of the spine, humerus, forearm, wrist and hip. Table 1 showed that the incidence of major osteoporotic fractures was 1.78-fold higher in patients with systemic lupus erythematosus than the non-lupus group (1.63 vs 0.92 per 1000 person-years; 95% CI 1.27 to 2.51, p<0.001), which was compatible with previous studies in South Korea and in USA showing that the systemic lupus erythematosus group had a higher incidence of fractures compared with the non-lupus group.[4 5]

Falls and osteoporotic fractures are common and important public health issues. Both conditions place a serious burden on injured patients, with potential detriment to their life quality. Falls account for the most events of osteoporotic fractures. That is, the less the falls, the less the osteoporotic fractures. From a view of primary prevention, physicians who participate in care of patients with systemic lupus erythematosus should take into consideration the strategies on fall prevention. Therefore, the possibility of osteoporotic fractures might be further reduced among these high-risk patients. We agree with Orsolini *et al*'s comments that osteoporosis and fractures should be regarded as relevant comorbidities in patients with systemic lupus erythematosus.[3] Recommendations for the clinicians to prevent falls and osteoporotic fractures in patients with systemic lupus erythematosus are needed in future relevant guidelines.

Shih-Wei Lai ,[1,2] **Yu-Hung Kuo**,[3] **Kuan-Fu Liao**[4,5]

[1]College of Medicine, China Medical University, Taichung, Taiwan
[2]Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan
[3]Department of Research, Taichung Tzu Chi Hospital, Taichung, Taiwan
[4]College of Medicine, Tzu Chi University, Hualien, Taiwan
[5]Division of Hepatogastroenterology, Department of Internal Medicine, Taichung Tzu Chi Hospital, Taichung, Taiwan

Correspondence to Dr Kuan-Fu Liao; kuanfuliaog@gmail.com

Contributors S-WL contributed to the conception of the article, initiated the draft of the article and has approved the final draft submitted. Y-HK and K-FL conducted data analysis.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Lai S-W, Kuo Y-H, Liao K-F. *Ann Rheum Dis* 2021;**80**:e179.

Received 2 October 2019
Accepted 5 October 2019
Published Online First 14 October 2019

Ann Rheum Dis 2021;**80**:e179. doi:10.1136/annrheumdis-2019-216417

ORCID iD
Shih-Wei Lai http://orcid.org/0000-0002-7420-1572

REFERENCES

1 Chung W-S, Lin C-L, Chang S-N, *et al*. Systemic lupus erythematosus increases the risks of deep vein thrombosis and pulmonary embolism: a nationwide cohort study. *J Thromb Haemost* 2014;12:452–8.
2 Hsu C-Y, Chen H-J, Hsu CY, *et al*. Splenectomy increases the subsequent risk of systemic lupus erythematosus. *Rheumatol Int* 2016;36:271–6.
3 Orsolini G, Bultink IEM, Adami G, *et al*. Bone health, an often forgotten comorbidity in systemic lupus erythematosus: a comment on the new recommendations. *Ann Rheum Dis* 2020;79:e150.
4 Kim CS, Han K-D, Jung JH, *et al*. Incidence and risk factors for osteoporotic fractures in patients with systemic lupus erythematosus versus matched controls. *Korean J Intern Med* 2019.
5 Tedeschi SK, Kim SC, Guan H, *et al*. Comparative Fracture Risks Among United States Medicaid Enrollees With and Those Without Systemic Lupus Erythematosus. *Arthritis Rheumatol* 2019;71:1141–6.
6 Ministry of Health and Welfare Taiwan. Taiwan health and welfare report, 2018. Available: http://www.mohw.gov.tw [Accessed 1 Oct 2019].
7 Lai S-W, Lin C-L, Liao K-F. Proton pump inhibitors therapy and the risk of major osteoporotic nonhip fractures in older adults in Taiwan. *Eur J Gastroenterol Hepatol* 2019;31:272–3.

Table 1 Incidences of major osteoporotic fractures between systemic lupus erythematosus group and non-systemic lupus erythematosus group in patients ≥40 years in 2005–2012

	Systemic lupus erythematosus				Non-systemic lupus erythematosus					
Variable	N	Event	Person-years	Incidence	N	Event	Person-years	Incidence	Incidence rate ratio (95% CI)	P value
All	566	33	2021	1.63	306 866	21 218	2 314 298	0.92	1.78 (1.27 to 2.51)	<0.001

Incidence per 1000 person-years
*Incidence rate ratio: systemic lupus erythematosus versus non-systemic lupus erythematosus (95% CI).

Association between osteoporosis and statins therapy

Statins therapy is found to be associated with a decreased risk of osteoporosis.[1 2] Moreover, a number of observational studies reported that statins therapy was associated with a decreased risk of osteoporotic fractures,[3 4] but other studies did not.[5 6] Some points are discussed here.

First, a study conducted by Leutner *et al*[7] published in *Annals of the Rheumatic Diseases* reported that low dose of statins therapy was associated with a decreased risk of osteoporosis, but high dose of statins therapy was associated with an increased risk of osteoporosis. Second, osteoporosis is often under-diagnosed and under-treated,[8] even though it might cause serious clinical problems and even though multiple effective medications are available now. Osteoporosis has placed some populations at risk of osteoporotic fractures. Leutner *et al*'s study gives a hint that high dose of statins therapy correlates with the risk of osteoporosis and maybe subsequent fractures. However, a cohort study reported that people taking high-potency statins such as atorvastatin or rosuvastatin were at lower risk of developing osteoporotic fractures when compared with those taking simvastatin.[3] A case–control study by Cheng *et al* reported that current use of statins seemed to have a protective effect against hip fracture in older people (adjusted OR 0.73, 95% CI 0.65 to 0.82).[4] There was also a dose-dependent effect of statins use on the protective effect of hip fracture in Cheng *et al*'s study.[4] That is, the higher the dose of statins use, the lower the risk of hip fracture. This finding was not compatible with Leutner *et al*'s study showing that high dose of statins use was associated with an increased risk of osteoporosis.[7] Third, blood lipid and bone mineral density are dynamic change. In clinical practice, the initial levels of blood lipid would determine which potency of statins should be used. Once the treatment goal of blood lipid is achieved, the dose of statins can be reduced. If the treatment goal is not achieved, the dose of statins can be increased. In addition, bone mineral density cannot be measured every day. It is difficult to assess that bone mineral density is affected by low dose or high dose of statins in retrospective studies. Only randomised controlled trials have a chance to investigate whether the dosage or the potency of statins would affect bone mineral density. Then the causation between statins therapy and osteoporosis can be clarified. Fourth, currently there is no research to definitely prove the causal relationship between statins therapy and osteoporosis. The US Preventive Services Task Force does not recommend that persons on statins therapy should screen for osteoporosis to prevent osteoporotic fractures.[9] It indicates that at present persons taking statins do not need to worry about the risk of osteoporosis. Finally, I agree with Leutner *et al*'s comments that future studies should focus on the causal relationship between the dosage-potency of statins and osteoporosis rather than the association.

Shih-Wei Lai [1,2]

[1]College of Medicine, China Medical University, Taichung, Taiwan
[2]Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan

Correspondence to Dr Shih-Wei Lai, Family Medicine, China Medical University Hospital, 404 Taichung City, Taiwan; wei@mail.cmuh.org.tw

Handling editor Josef S Smolen

Contributors S-WL contributed to the conception of the article, initiated the draft of the article and has approved the final draft submitted.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Lai S-W. *Ann Rheum Dis* 2021;**80**:e180.

Received 10 October 2019
Accepted 13 October 2019
Published Online First 25 October 2019

Linked

► http://dx.doi.org/10.1136/annrheumdis-2019-216494

Ann Rheum Dis 2021;**80**:e180. doi:10.1136/annrheumdis-2019-216464

ORCID iD
Shih-Wei Lai http://orcid.org/0000-0002-7420-1572

REFERENCES

1 Lin T-K, Chou P, Lin C-H, *et al*. Long-Term effect of statins on the risk of new-onset osteoporosis: a nationwide population-based cohort study. *PLoS One* 2018;13:e0196713.
2 Lin S-M, Wang J-H, Liang C-C, *et al*. Statin use is associated with decreased osteoporosis and fracture risks in stroke patients. *J Clin Endocrinol Metab* 2018;103:3439–48.
3 Lin T-K, Liou Y-S, Lin C-H, *et al*. High-Potency statins but not all statins decrease the risk of new-onset osteoporotic fractures: a nationwide population-based longitudinal cohort study. *Clin Epidemiol* 2018;10:159–65.
4 Cheng K-C, Liao K-F, Lin C-L, *et al*. Case-Control study examining the association between hip fracture risk and statins therapy in old people. *Medicine* 2019;98:e17476.
5 Peña JM, Aspberg S, MacFadyen J, *et al*. Statin therapy and risk of fracture: results from the JUPITER randomized clinical trial. *JAMA Intern Med* 2015;175:171–7.
6 van Staa TP, Wegman S, de Vries F, *et al*. Use of statins and risk of fractures. *JAMA* 2001;285:1850–5.
7 Leutner M, Matzhold C, Bellach L, *et al*. Diagnosis of osteoporosis in statin-treated patients is dose-dependent. *Ann Rheum Dis* 2019;78:1706–11.
8 Nayak S, Roberts MS, Greenspan SL. Factors associated with diagnosis and treatment of osteoporosis in older adults. *Osteoporos Int* 2009;20:1963–7.
9 Curry SJ, Krist AH, Owens DK, *et al*. Screening for osteoporosis to prevent fractures: US preventive services Task force recommendation statement. *JAMA* 2018;319:2521–31.

Response to: 'Association between osteoporosis and statins therapy' by Lai

We read with interest the correspondence of Lai .[1] Whether statin therapy impacts the risk of osteoporosis is still a matter of debate. We have recently shown that there is a dose-dependent relationship between statins and diagnosis of osteoporosis; while low-dose statin treatment was related to an underrepresentation of diagnosed osteoporosis when compared with non-statin-treated patients, we found in patients on higher dosages of statins an overrepresentation of diagnosed osteoporosis in the general Austrian population.[2] Although osteoporosis is often underdiagnosed until incident fractures, our data are based on diagnoses derived from in-patient treatment. Even though there are data available suggesting that some statins could have protective effects on osteoporosis,[3] in the JUPITER trial, an international, randomised, double-blind and placebo-controlled study in which 17 802 patients were investigated, it has been shown that high-potency statin treatment did not reduce the risk of fractures.[4] The fact that statin treatment might not only have positive effects on bone health has also been demonstrated in a Women's Health Initiative Observational Study in which 93 716 postmenopausal women with simvastatin and atorvastatin treatment showed an HR of 1.42 (0.79–2.57) for hip fracture and did not show improved bone mineral density (BMD) when compared with controls. Interestingly, in this study, statins of higher potency were related to a higher risk of hip fracture when compared with statins with lower potency such as pravastatin, fluvastatin and lovastatin.[5] A study by Lin *et al* also showed not only positive effects on new-onset osteoporotic fractures, but also demonstrated a trend for a higher risk under lovastatin treatment.[3] A comparison of our results to previous findings is problematic due to other studies not considering the detailed different dosages of the respective statins.[3] It is indeed a well-known statistical phenomenon that a trend that appears in different groups of data (eg, groups of statins) may disappear or even reverse after combining the groups, the so-called Simpson's paradox.[6] A recently published study by Cheng *et al* investigating 7464 patients with newly diagnosed hip fractures showed that a statin treatment with a dosage higher than 15 mg (OR: 0.71, CI 0.61 to 0.82), as well as lower than 15 mg (OR: 0.75, CI 0.65 to 0.88) was related to a lower risk of hip fractures in comparison to non-statin-treated patients, but they did not investigate the different kinds of statins and their exact dosages in detail.[7] Despite limited comparability to the study by Cheng *et al*, we, for instance, also found an underrepresentation for doses of up to 20 mg of fluvastatin in our recently published study. In addition, dosages of >10–20 mg of the most potent statin, rosuvastatin, also showed a tendency towards an underrepresentation of osteoporosis; however, these results were not statistically significant in our study.[2] We do not agree with the argument of Lai *et al* that when the treatment goal of blood lipids is achieved, the dose of statins can be decreased. Guidelines do not recommend reducing statin dosage when the treatment goal is achieved; on the contrary, the current credo is 'the lower the better' for low density lipoprotein (LDL) cholesterol mirrored in recently published European Society of Cardiology/European Atherosclerosis Society guidelines on the management of dyslipidemias recommending lowering LDL cholesterol levels <55 mg/dL in high-risk patients.[8] This goal is very difficult to achieve with a reduction in the statin dose. The cardiovascular advantage of low LDL cholesterol levels in patients of high cardiovascular risk is also evidenced by recent studies on PCSK9 inhibitors which even achieve lower cholesterol levels but without impact on sex hormones.[9]

However, especially the discrepancies in the currently existing data regarding the relationship between statins and osteoporosis and the sparse data about the different kinds of statins and their exact dosages was one of the major reasons for the present study to investigate this relevant topic in more detail. Thus, one has to keep in mind that cholesterol is the basic substance for vital hormones such as estrogens, testosterone, cortisol or aldosterone and several studies have shown that, for example, statins can lower the levels of sex hormones.[10–14] These vital hormones are closely related to several diseases. Hence, especially the relationship between high-dosage statin treatment and the different potencies and potentially related diseases such as osteoporosis or cancer should be investigated in prospective clinical studies and randomised controlled trials.

Michael Leutner,[1] Caspar Matzhold,[2,3] Luise Bellach,[1] Carola Deischinger,[1] Jürgen Harreiter,[1] Stefan Thurner,[2,3,4,5] Peter Klimek,[2,3] Alexandra Kautzky-Willer [1]

[1]Department of Internal Medicine III, Clinical Division of Endocrinology and Metabolism, Unit of Gender Medicine, Medical University of Vienna, Vienna, Austria
[2]Section for Science of Complex Systems, CeMSIIS, Medical University of Vienna, Vienna, Austria
[3]Complexity Science Hub Vienna, Vienna, Austria
[4]Santa Fe Institute, Santa Fe, NM, USA
[5]IIASA, Laxenburg, Austria

Correspondence to Professor Alexandra Kautzky-Willer, Internal Medicine III, Division of Diabetology, Medical University of Vienna, 1090 Wien, Austria; alexandra.kautzky-willer@meduniwien.ac.at

Handling editor Josef Smolen

Contributors Study design: ML, CM, ST, PK and AK-W. Manuscript writing: ML, PK and AK-W. All authors read, reviewed and approved the final manuscript.

Funding This study was funded by WWTF (MA16-045).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Leutner M, Matzhold C, Bellach L, *et al*. *Ann Rheum Dis* 2021;**80**:e181.

Received 17 October 2019
Accepted 20 October 2019
Published Online First 25 October 2019

Linked

► http://dx.doi.org/10.1136/annrheumdis-2019-216464

Ann Rheum Dis 2021;**80**:e181. doi:10.1136/annrheumdis-2019-216494

ORCID iD
Alexandra Kautzky-Willer http://orcid.org/0000-0002-3520-4105

REFERENCES

1 Lai SW. The association between osteoporosis and statins therapy. *Ann Rheum Dis* 2021;80:e180.
2 Leutner M, Matzhold C, Bellach L, *et al*. Diagnosis of osteoporosis in statin-treated patients is dose-dependent. *Ann Rheum Dis* 2019;78:1706–11.
3 Lin T-K, Liou Y-S, Lin C-H, *et al*. High-Potency statins but not all statins decrease the risk of new-onset osteoporotic fractures: a nationwide population-based longitudinal cohort study. *Clin Epidemiol* 2018;10:159–65.
4 Pena JM, Aspberg S, MacFadyen J, *et al*. Statin therapy and risk of fracture: results from the JUPITER randomized clinical trial. *JAMA Intern Med* 2015;175:171–7.

5 LaCroix AZ, Cauley JA, Pettinger M, *et al*. Statin use, clinical fracture, and bone density in postmenopausal women: results from the women's health Initiative observational study. *Ann Intern Med* 2003;139:97–104.
6 Julious SA, Mullee MA. Confounding and Simpson's paradox. *BMJ* 1994;309:1480–1.
7 Cheng K-C, Liao K-F, Lin C-L, *et al*. Case-Control study examining the association between hip fracture risk and statins therapy in old people. *Medicine* 2019;98:e17476.
8 Mach F, Baigent C, Catapano AL, *et al*. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2019;37.
9 Blom DJ, Djedjos CS, Monsalvo ML, *et al*. Effects of evolocumab on vitamin E and steroid hormone levels: results from the 52-week, phase 3, double-blind, randomized, placebo-controlled Descartes study. *Circ Res* 2015;117:731–41.
10 Corona G, Boddi V, Balercia G, *et al*. The effect of statin therapy on testosterone levels in subjects consulting for erectile dysfunction. *J Sex Med* 2010;7:1547–56.
11 de Keyser CE, de Lima FV, de Jong FH, *et al*. Use of statins is associated with lower serum total and non-sex hormone-binding globulin-bound testosterone levels in male participants of the Rotterdam study. *Eur J Endocrinol* 2015;173:155–65.
12 Stanworth RD, Kapoor D, Channer KS, *et al*. Statin therapy is associated with lower total but not bioavailable or free testosterone in men with type 2 diabetes. *Diabetes Care* 2009;32:541–6.
13 Schooling CM, Au Yeung SL, Freeman G, *et al*. The effect of statins on testosterone in men and women, a systematic review and meta-analysis of randomized controlled trials. *BMC Med* 2013;11:57.
14 Zhang X, Li J, Zhou X, *et al*. Simvastatin decreases sex hormone levels in male rats. *Endocr Pract* 2017;23:175–81.

Anti-Ku antibodies: important points to consider

With interest, we read the recent article by Ogawa-Momohara *et al*[1] which reports the clinical phenotype of patients with anti-Ku autoantibodies and conclude that systemic lupus erythematosus (SLE) and myositis overlap is rare in patients with this antibody reactivity. Ku is a well-known protein heterodimer comprised of 70 and 80 kDa subunits and is best-known for its central role in binding to DNA and the double-strand break DNA repair pathway in mammals.[2]

There are several challenges when describing the clinical phenotype of patients with anti-Ku antibodies. First, as noted above, Ku is a DNA-binding protein. Consequently, it is difficult but imperative to confirm that patients who test positive for anti-Ku antibodies truly have anti-Ku antibodies, or if the reactivity is caused by antibodies to dsDNA or DNA-binding proteins that are complexed with dsDNA/dsDNA-binding proteins in the serum of patients that then secondarily bind to Ku or dsDNA/dsDNA-binding proteins in an immunoassay (figure 1). In this context, Reeves *et al*[3] demonstrated that anti-Ku reactivity of certain sera as detected by enzyme linked immunoassay Intenrational consensus on antinuclear antibody (ANA) pattern (ELISA) disappeared when the Ku antigen was dissociated from DNA after washing with 0.5 M or higher NaCl buffer, indicating that the reactivity of these sera was via binding of DNA and DNA-binding proteins to Ku. Interaction of various dsDNA-binding proteins complexed with Ku was also reported.[4] Thus, an analytically false positive anti-Ku ELISA result can be observed if DNA and other DNA-binding proteins are binding to Ku on the ELISA plate. The same concept applies to other solid phase immunoassays for the detection of anti-Ku antibodies, such as line immunoassays, which are commonly used in clinical laboratory practice. Noteworthy, a similar challenge also exists for anti-Scl-70/topoisomerase I antibodies, a marker that is considered specific for systemic sclerosis, but depending on the assay is also detected in patients with SLE.[5] Although known for decades, very little data are available on the standardisation of anti-Ku antibodies. In a recent study, a *kappa* agreement of 0.86 (95% CI 0.57 to 1.00) was found indicating weak-to-perfect agreement.[6 7]

In addition, if patients are preselected based on HEp-2 indirect immunofluorescence (IIF) patterns, a potential exclusion bias is introduced (figure 2). In the correspondence by Ogawa-Momohara *et al*,[1] samples were preselected based on the HEp-2 IIF pattern that has been historically associated with anti-Ku antibodies (ICAP nomenclature AC-04; www.anapatterns.org).[8] This approach introduces a potential bias because patients with SLE frequently express many autoantibodies[9] and sera accompanied by mixed HEp-2 IIF patterns are very common and presumably were excluded in this study. Therefore, the conclusion that overlap syndrome in anti-Ku-positive patients is rare might not reflect the entire picture. In our experience, anti-Ku antibodies are frequently found in SLE patients potentially associated with overlap features of a myopathy.[10] Similarly, anti-Ku antibodies are known as autoantibodies that mark the overlap between myositis and systemic sclerosis.[11]

The observation that a significant portion of anti-Ku-positive patients also exhibit anti-dsDNA antibodies is complicated by the known variability between anti-dsDNA assays.[12] In the correspondence by Ogawa-Momohara *et al*,[1] no information is

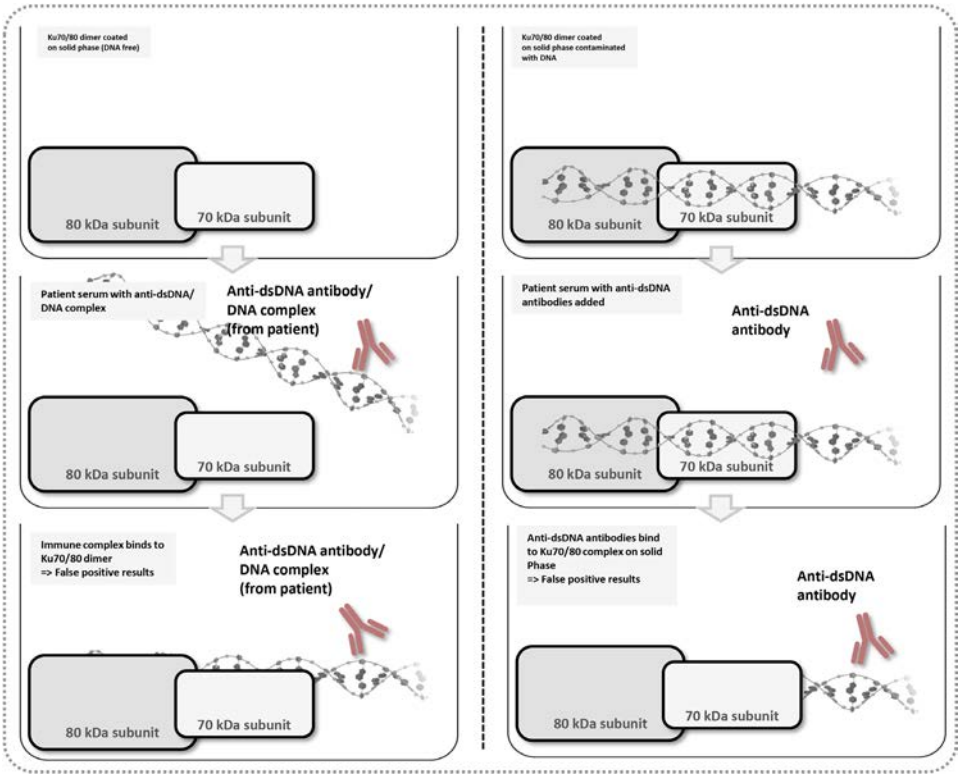


Figure 1 Potential reactivity of anti-dsDNA antibodies in anti-Ku antibody assays. The Ku70/80 heterodimer exhibits dsDNA binding capacities. Consequently, if the antigen used in the Ku assay contains dsDNA, anti-dsDNA antibodies can also bind directly to the Ku70/80-dsDNA complex on the solid phase. In addition, anti-dsDNA/dsDNA complexes that might be present in the sera of patients with autoimmune diseases can generate a positive test result. In addition, other DNA-binding proteins can bind to DNA or the Ku70/80-DNA complex and also serve as autoantigenic targets (not shown for simplicity).

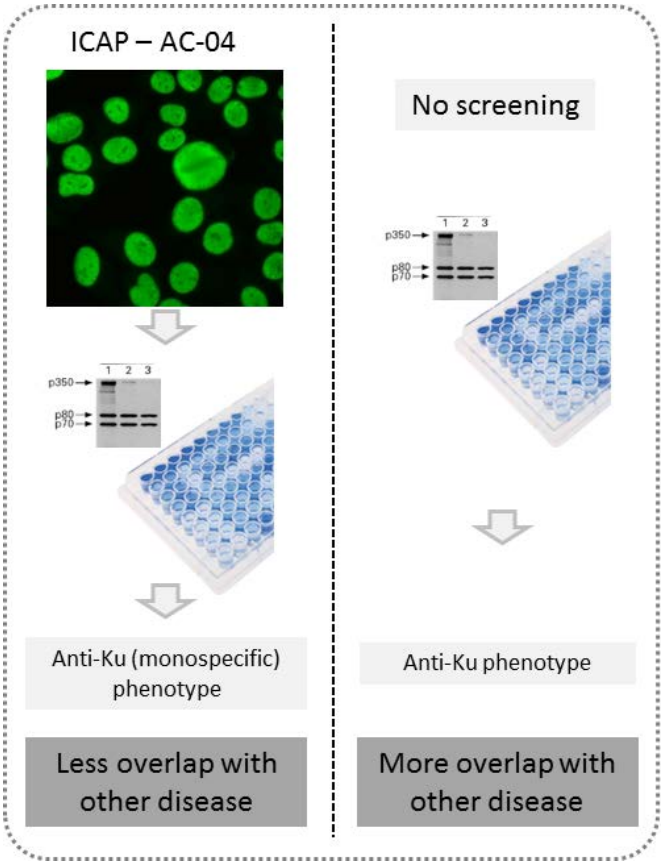


Figure 2 Potential selection bias based on the HEp-2 indirect immunofluorescence (IIF) pattern. The ICAP AC-04 IIF pattern which can be related to anti-Ku antibodies is characterised by fine tiny speckles throughout the nucleoplasm. The nucleoli may or may not be stained. The chromatin mass of mitotic cells (metaphase, anaphase and telophase) is not stained. According to ICAP, other autoantibodies, such as SS-A/Ro60, SS-B/La, Mi-2, TIF1γ and TIF1β, can produce a similar IIF pattern. In addition, autoantibodies, such as anti-dsDNA or anti-chromatin antibodies, can mask or confuse the ICAP AC-4 pattern potentially leading to the selection of mostly monospecific anti-Ku antibodies that might not show overlap features.

provided on the methods used for the detection of anti-dsDNA and anti-ssDNA antibodies. Therefore, the interpretation of the results in this study is difficult. Unexpectedly, anti-dsDNA reactivity was found predominantly in myositis and not in SLE patients. Noteworthy, recently a novel standard for anti-dsDNA antibodies has been developed and characterised which interestingly also seems to contain anti-Ku reactivity.[13] However, studies are pending to ensure that the new anti-dsDNA standard truly contains antibodies to the Ku70/80 heterodimeric complex and not only high levels of anti-dsDNA antibodies or immune complexes that generate positivity in anti-Ku immunoassays. This may or may not represent a link to the two different clusters of anti-Ku antibodies that have been described and also controversially discussed.[14–18]

To conclude, we emphasise that defining the clinical phenotype associated with anti-Ku antibodies is challenging and should be based on a systemic study considering all the aforementioned points raised . In particular, selection of serum samples based on a HEp-2 IIF staining pattern does not capture the full spectrum of the clinical associations of this interesting autoantibody.

Michael Mahler ,[1] **Minoru Satoh,**[2] **Marvin J Fritzler**[3]

[1]Research, Inova Diagnostics, San Diego, California, USA
[2]Department of Clinical Nursing, University of Occupational and Environmental Health, Kitakyushu, Japan
[3]Medicine, Health Sciences Centre, Calgary, Alberta, Canada

Correspondence to Dr Michael Mahler, Research, INOVA Diagnostics, San Diego, CA 32131-1638, USA; mmahler@inovadx.com

Contributors All the authors contributed to the generation of the manuscript. MM drafted the manuscript, coordinated revisions and generated figures. MS provided insights into the cross-reactivity of interference between anti-Ku and anti-dsDNA antibodies. MJF revised the manuscript and provided details around HEp-2 pattern and potential bias for the definition of the clinical phenotype.

Competing interests MM is an employee of Inova Diagnostics, a company commercialising antibody assays. MJF is a consultant to Inova Diagnostics (San Diego, California, USA) and Werfen International (Barcelona, Spain). No products of Inova Diagnostics are being discussed in the manuscript.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Mahler M, Satoh M, Fritzler MJ. *Ann Rheum Dis* 2021;**80**:e182.

Received 24 October 2019
Revised 29 October 2019
Accepted 1 November 2019
Published Online First 20 November 2019

Linked

► http://dx.doi.org/10.1136/annrheumdis-2019-216595

Ann Rheum Dis 2021;**80**:e182. doi:10.1136/annrheumdis-2019-216535

ORCID iD
Michael Mahler http://orcid.org/0000-0002-7919-0948

REFERENCES

1 Ogawa-Momohara M, Muro Y, Akiyama M. Overlap of systemic lupus erythematosus and myositis is rare in anti-Ku antibody-positive patients. *Ann Rheum Dis* 2021;80:e147.
2 Fell VL, Schild-Poulter C. The Ku heterodimer: function in DNA repair and beyond. *Mutat Res Rev Mutat Res* 2015;763:15–29.
3 Reeves WH, Satoh M, Wang J, *et al*. Systemic lupus erythematosus. antibodies to DNA, DNA-binding proteins, and histones. *Rheum Dis Clin North Am* 1994;20:1–28.
4 Satoh M, Ajmani AK, Stojanov L, *et al*. Autoantibodies that stabilize the molecular interaction of Ku antigen with DNA-dependent protein kinase catalytic subunit. *Clin Exp Immunol* 1996;105:460–7.
5 Mahler M, Silverman ED, Schulte-Pelkum J, *et al*. Anti-Scl-70 (topo-I) antibodies in SLE: myth or reality? *Autoimmun Rev* 2010;9:756–60.
6 Mahler M, Vulsteke J-B, Bossuyt X, *et al*. Standardisation of myositis-specific antibodies: where are we today? *Ann Rheum Dis* 2019. doi:10.1136/annrheumdis-2019-216003. [Epub ahead of print: 3 Aug 2019].
7 Espinosa-Ortega F, Holmqvist M, Alexanderson H, *et al*. Comparison of autoantibody specificities tested by a line blot assay and immunoprecipitation-based algorithm in patients with idiopathic inflammatory myopathies. *Ann Rheum Dis* 2019;78:858–60.
8 Damoiseaux J, Andrade LEC, Carballo OG, *et al*. Clinical relevance of HEp-2 indirect immunofluorescent patterns: the International Consensus on ANA patterns (ICAP) perspective. *Ann Rheum Dis* 2019;78:879–89.
9 Yaniv G, Twig G, Shor DB-A, *et al*. A volcanic explosion of autoantibodies in systemic lupus erythematosus: a diversity of 180 different antibodies found in SLE patients. *Autoimmun Rev* 2015;14:75–9.
10 Mahler M, Swart A, Wu J, *et al*. Clinical and serological associations of autoantibodies to the Ku70/Ku80 heterodimer determined by a novel chemiluminescent immunoassay. *Lupus* 2016;25:889–96.
11 Kaji K, Fertig N, Medsger TA, *et al*. Autoantibodies to RuvBL1 and RuvBL2: a novel systemic sclerosis-related antibody associated with diffuse cutaneous and skeletal muscle involvement. *Arthritis Care Res* 2014;66:575–84.
12 Mummert E, Fritzler MJ, Sjöwall C, *et al*. The clinical utility of anti-double-stranded DNA antibodies and the challenges of their determination. *J Immunol Methods* 2018;459:11–19.

13 Fox BJ, Hockley J, Rigsby P, *et al*. A WHO reference reagent for lupus (anti-dsDNA) antibodies: international collaborative study to evaluate a candidate preparation. *Ann Rheum Dis* 2019;78:1677–80.
14 Spielmann L, Nespola B, Séverac F, *et al*. Anti-Ku syndrome with elevated CK and anti-Ku syndrome with anti-dsDNA are two distinct entities with different outcomes. *Ann Rheum Dis* 2019;78:1101–6.
15 Spielmann L, Séverac F, Meyer A. The heart of anti-Ku related disease: extensive review and meta-analysis. Response to: 'Anti-Ku syndrome with elevated CK: association with myocardial involvement in systemic sclerosis' by Campochiaro *et al*. *Ann Rheum Dis* 2021;80:e114.
16 Mahler M, Rossin B, Kubassova O. Augmented versus artificial intelligence for stratification of patients with myositis. *Ann Rheum Dis* 2020;79:e162.
17 Pinal-Fernandez I, Mammen AL. On using machine learning algorithms to define clinically meaningful patient subgroups. *Ann Rheum Dis* 2020;79:e128.
18 Meyer A, Spielmann L, Séverac F. Artificial intelligence should always be guided by human intelligence. Response to 'Augmented vs. artificial intelligence for stratification of patients with myositis' by Mahler *et al*. *Ann Rheum Dis* 2020;79:e163.

Response to: 'Anti-Ku antibodies: important points to consider' by Mahler *et al*

We thank the authors[1] for their interest in our paper[2] and are grateful for the opportunity to respond to the points raised. We agree with the opinion of Mahler *et al* that 'SLE frequently express many autoantibodies and sera accompanied by mixed HEp-2 IIF pattern were very common'. We adopted the same methods for anti-Ku screening that Spielmann *et al*[3] used in their study to avoid missing multiple autoantibody-positive cases. The Spielmann group included ANA-positive sera showing several ANA patterns (ICAP nomenclature: AC-1, AC-4 or AC-5) for ELISA analysis.

Although Mahler *et al* noted that 'In our experience, anti-Ku antibodies are frequently found in SLE patients potentially associated with overlap features of a myopathy', of the four anti-Ku antibody-positive myositis patients in their referenced study, only two patients had systemic lupus erythematosus (SLE) overlapping with myositis.[3] Given that 33 anti-Ku-positive SLE patients in their study[4] did not have myositis, it seems that SLE and myositis are less likely to overlap. We need to be careful in discussing the frequency of anti-Ku-associated clinical phenotypes.

We detected anti-dsDNA and anti-ssDNA antibodies by using two commercial ELISA kits (MBL, Nagoya, Japan). These kits are commonly used in Japan and are covered by health insurance for clinical laboratory tests. As Mahler *et al* noted that there is variability between anti-dsDNA assays,[1] we need to use immunofluorescence tests with *Crithidia luciliae* as a substrate for confirmation.

Mariko Ogawa-Momohara,[1] Yoshinao Muro ,[2] Masashi Akiyama[2]

[1]Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Nagoya, Japan
[2]Dermatology, Nagoya University, Nagoya, Japan

Correspondence to Dr Yoshinao Muro, Dermatology, Nagoya University, Nagoya, Japan; ymuro@med.nagoya-u.ac.jp

Handling editor Josef S Smolen

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Ogawa-Momohara M, Muro Y, Akiyama M. *Ann Rheum Dis* 2021;**80**:e183.

Received 8 November 2019
Revised 8 November 2019
Accepted 11 November 2019
Published Online First 20 November 2019

Linked

► http://dx.doi.org/10.1136/annrheumdis-2019-216535

Ann Rheum Dis 2021;**80**:e183. doi:10.1136/annrheumdis-2019-216595

ORCID iD
Yoshinao Muro http://orcid.org/0000-0003-2329-8375

REFERENCES

1 Mahler M, Satoh M, Fritzler MJ. Anti-Ku antibodies: important points to consider. *Ann Rheum Dis* 2021;80:e182.
2 Ogawa-Momohara M, Muro Y, Akiyama M. Overlap of systemic lupus erythematosus and myositis is rare in anti-Ku antibody-positive patients. *Ann Rheum Dis* 2021;80:e147.
3 Spielmann L, Nespola B, Séverac F, *et al*. Anti-Ku syndrome with elevated CK and anti-Ku syndrome with anti-dsDNA are two distinct entities with different outcomes. *Ann Rheum Dis* 2019;78:1101–6.
4 Mahler M, Swart A, Wu J, *et al*. Clinical and serological associations of autoantibodies to the Ku70/Ku80 heterodimer determined by a novel chemiluminescent immunoassay. *Lupus* 2016;25:889–96.

Temporal ultrasound for monitoring tocilizumab treatment in giant cell arteritis: seeing beyond serum markers?

We read with great interest the letter of Nannini *et al*, which addressed the issue of treatment interruption in giant cell arteritis (GCA) patients treated with tocilizumab (TCZ) and the use of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) for disease monitoring and relapse predicting.[1] In this study, FDG-PET examination after 2 months of TCZ discontinuation (14 months after treatment initiation) could identify those large-vessel GCA (LV-GCA) patients who would experience a relapse later, despite having normal inflammation markers. Interestingly, FDG-PET findings after 6 months of TCZ therapy were not significantly improved in patients who relapsed after TCZ discontinuation, in contrast to what was observed for those who maintained remission.[1] According to authors, this imaging modality could be a useful monitoring and prognostic tool for patients with LV-GCA.

GCA, a type of large-size and medium-size vessel vasculitis, usually affects people over 50 years old. Two subtypes have been identified; namely cranial GCA and LV-GCA. Over the last years, ultrasound (US) of temporal arteries has been increasingly recognised as a first-line diagnostic tool for cranial GCA, while magnetic-resonance angiography and FDG-PET are utilised for the diagnosis of LV-GCA. Moreover, randomised controlled trials in GCA patients have shown that the addition of TCZ to corticosteroids induces disease remission and offers faster steroid sparing and reduced relapse rate. On the other hand, nearly one-third of patients treated with TCZ might experience a disease flare after treatment discontinuation,[1] while clinical and serological parameters might fail to reveal a disease relapse.[2] In addition, TCZ treatment leads to a fall of inflammation markers that sometimes does not reflect disease activity.[3] Due to the lack of reliable serological marker for these patients, imaging modalities emerge as possible monitoring and prognostic tools. Repeated biopsies for disease monitoring are not feasible in clinical practice.

Regarding the cranial form of GCA, FDG-PET is high-cost, has low availability, exposes the patient to ionising radiation and has questionable sensitivity in this form of the disease. In contrast, US has low cost, is generally available, bears no radiation and offers acceptable sensitivity in the detection of vessel wall inflammation in temporal arteries. On this basis, serial US examinations might be useful for the monitoring of TCZ treatment.

The experience about temporal US in cranial GCA patients treated with TCZ is limited. Vitiello *et al* reported two cases in which initiation of TCZ treatment led to disappearance of 'halo sign' in the temporal US.[4] In our clinic, TCZ resulted in significant amelioration of vessel wall inflammation in two cases. TCZ was initiated in a 62-year-old woman with cranial GCA. The baseline temporal US revealed a hypoechoic halo sign in both superficial common temporal arteries (figure 1A). A new temporal US 3 months later showed decrease of the hypoechoic area in the vessel wall, while clinical and serological improvement was evident (figure 1B). After 12 months of TCZ treatment, the patient is in disease remission and the hypoechoic findings in the vessel wall have almost disappeared (figure 1C). Additionally, in an 85-year-old woman with cranial GCA, TCZ led to improvement of the hypoechoic appearance of the inflamed vessel wall, as depicted in a new temporal US performed 3 months after treatment commencement, compared with baseline.

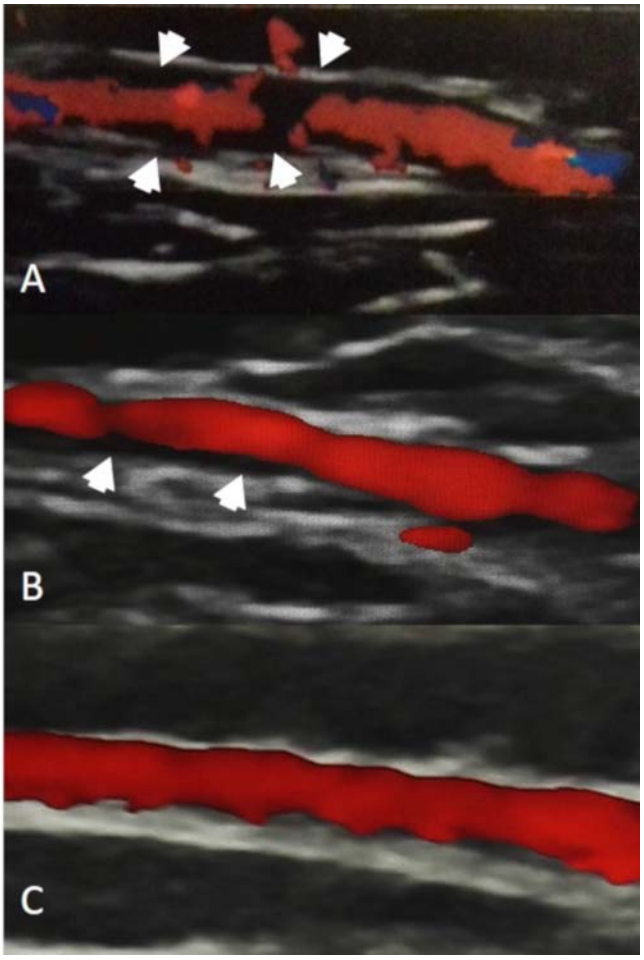


Figure 1 Ultrasound of the right superficial common temporal artery (longitudinal view) at baseline (A), 3 months later (B) and 12 months after (C) consecutive tocilizumab treatment. At baseline (A), a dark hypoechoic area can be noted at the vessel wall (arrows). Three months later, the 'halo sign' has been improved (B) and after 12 months it has almost disappeared (C). Meanwhile, serum inflammation markers and patient's symptoms have significantly improved. A linear probe (12 L), 12 MHz (grey scale) and 6.7 MHz (colour Doppler) frequency were used.

As for LV-GCA, the wall of large vessels might remain thickened for months despite therapy, but an increase in intima-media complex, as observed by US, suggests treatment failure.[5] It has been reported that contrast-enhanced US can detect disease flares in patients treated with TCZ for Takayasu arteritis, but this US technique has not been extensively studied yet. Therefore, the use of US in the monitoring of patients with LV-GCA is still under debate. Based on the letter of Nannini *et al*, FDG-PET might be useful in monitoring TCZ-treated patients with LV-GCA. A question arising is whether findings in US parallel the changes depicted in FDG-PET. We believe that a comparative study addressing this issue would be of great interest.

Recently, the role of US in the follow-up of GCA patients has emerged.[6] As US is an operator-dependent examination, the objectivity of repetitive examinations is questionable and the technical parameters should be precisely determined. Awaiting further prospective studies, we suggest that temporal US can be an appealing choice for monitoring disease activity in cranial GCA patients treated with TCZ.

Gerasimos Evangelatos [1], **George E Fragoulis** [2], **Alexios Iliopoulos**[1]

[1]Rheumatology Department, 417 Army Share Fund Hospital (NIMTS), Athens, Greece
[2]Rheumatology Unit, First Department of Propaedeutic Internal Medicine, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

Correspondence to Dr Gerasimos Evangelatos, Rheumatology Department, 417 Army Share Fund Hospital (NIMTS), 115 21 Athens, Greece; gerevag@gmail.com

Twitter George E Fragoulis @FragoulisGeorge

Contributors GE: performed the ultrasound examinations, took photo of the ultrasounds, participated in literature search and manuscript preparation, approved the final version of the manuscript. GEF: participated in literature search and manuscript preparation, approved the final version of the manuscript. AI: participated in manuscript preparation and approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Evangelatos G, Fragoulis GE, Iliopoulos A. *Ann Rheum Dis* 2021;**80**:e184.

Received 23 October 2019
Accepted 30 October 2019
Published Online First 5 November 2019

Ann Rheum Dis 2021;**80**:e184. doi:10.1136/annrheumdis-2019-216527

ORCID iDs
Gerasimos Evangelatos http://orcid.org/0000-0003-3822-3093
George E Fragoulis http://orcid.org/0000-0003-4932-7023

REFERENCES

1 Nannini C, Niccoli L, Sestini S, *et al*. Remission maintenance after tocilizumab dose-tapering and interruption in patients with giant cell arteritis: an open-label, 18-month, prospective, pilot study. *Ann Rheum Dis* 2019;78:1444–6.
2 Adler S, Reichenbach S, Gloor A, *et al*. Risk of relapse after discontinuation of tocilizumab therapy in giant cell arteritis. *Rheumatology* 2019;58:1639–43.
3 Stone JH, Tuckwell K, Dimonaco S, *et al*. Glucocorticoid dosages and acute-phase reactant levels at giant cell arteritis flare in a randomized trial of tocilizumab. *Arthritis Rheumatol* 2019;71:1329–38.
4 Vitiello G, Orsi Battaglini C, Carli G, *et al*. Tocilizumab in giant cell arteritis: a real-life retrospective study. *Angiology* 2018;69:763–9.
5 Schmidt WA. Ultrasound in the diagnosis and management of giant cell arteritis. *Rheumatology* 2018;57:ii22–31.
6 Monti S, Floris A, Ponte CB, *et al*. The proposed role of ultrasound in the management of giant cell arteritis in routine clinical practice. *Rheumatology* 2018;57:112–9.

Involvement of industry in review articles published in Annals of the Rheumatic Diseases

Specifically, I refer to the *Review Article* on IL-17A by McGonagle *et al*.[1] The article is excellent and reads very well, and the authors are highly acknowledged scientists and clinicians, some of them I know personally—nice colleagues and friends. Yet, I was puzzled to find out that the article was written by a professional medical writer sponsored by a company. Although all this information on funding and involvement of medical writers is transparantly provided in the article in the sections on acknowledgements, contributors and funding, the value of such a *Review Article* may change once the reader becomes aware of the involvement of pharmaceutical industry.

In *Review Articles* in highly accredited journals like *Annals of the Rheumatic Diseases*, authors express their views and interpretation of recent findings in the field, usually in a scientifically adequate and, importantly, pharmaceutical industry-independent way! Readers of such *Review Articles* expect a highly balanced, critical and objective review of the topic of choice. This expectation may not be met if the article is written by professional writers, paid by a company which manufactures a drug approved for a disease that is discussed in such an article.

Clinician rheumatologists are often involved in clinical trials, and all manuscripts on clinical trial data are usually prepared by professional writers hired by the companies, with authors commenting, often substantially, as the manuscript develops. Such a procedure is generally accepted by the scientific community, and it is also understandable since the data of the trial are in fact owned by the company. The situation with *Review Articles*, however, is strikingly different: if the motivation of such articles is driven by (economic) interests of a third party (industry), such an article gets a certain 'flavour'.

Apart from the principal concerns I have with *Review Articles* in *ARD* written by professional medical writers sponsored by industry, I provide a precise example from the article demonstrating potential risks: in figure 4 of the article on p1172[1], it is stated by a simple symbol that secukinumab is effective in many disease domains and manifestations including structural progression in the approved indications psoriasis, psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Although this aspect (structural progression) is not further discussed, neither in the main text nor in the legend of figure 4, the message from figure 4 for the reader is crystal clear: secukinumab inhibits structural progression in both PsA and in AS! As of to date, however, there is only indirect circumstantial and very limited information on potential effects of IL-17 blockade on structural progression in AS, similar to the limited and circumstantial evidence of anti-tumour necrosis factor (TNF) agents on inhibition of AS structural progression. The reported structural progression in AS patients treated with secukinumab over 2 and 4 years, respectively, was indeed low, but there was no comparator group in this trial (uncontrolled data).[2 3] In another paper on radiographic progression after 2 years of secukinumab treatment as compared with historical data from AS patients tretated with non-steroidal antiinflammatory drugs (NSAIDs) only, there was only a statistically non-significant trend for less progression in secukinumab-treated patients as compared with the historical cohort.[4] A head-to-head study on the effects of secukinumab on radiographic progression in AS with adalimumab as a comparator is ongoing but the results are not available yet. Accordingly, the current evidence on inhibition of strucutral progression by IL-17 is weak, yet figure 4 in the *Review Article*[1] suggests a clear inhibitory effect in both PsA and AS. This single example illustrates how apparant subtleties introduced intentionally or by mistake by professional medical writers may dramatically impact on the content and message of such *Review Article*.

I suggest to the editor and to the editorial board of the *Annals of the Rheumatic Diseases* to reconsider their policy of acceptance of *Review Articles* written by professional medical writers sponsored by industry.

Martin Rudwaleit

Correspondence to Professor Martin Rudwaleit, Internal Medicine and Rheumatology, Klinikum Bielefeld Rosenhöhe, 33647 Bielefeld, Germany; martin.rudwaleir@klinikumbielefeld.de

Contributors The author wrote this article without the contribution of other authors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests During the previous 10 years, the author received honoraria and/or consulting fees and/or travel and accomodation support at scientific meetings from AbbVie, BMS, Celgene, Chugai/Roche, Janssen, Eli Lilly, MSD, Novartis, Pfizer and UCB Pharma.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Rudwaleit M. *Ann Rheum Dis* 2021;**80**:e185.

Received 26 October 2019
Accepted 30 October 2019
Published Online First 22 November 2019

Linked

► http://dx.doi.org/10.1136/annrheumdis-2019-216568

Ann Rheum Dis 2021;**80**:e185. doi:10.1136/annrheumdis-2019-216544

ORCID iD
Martin Rudwaleit http://orcid.org/0000-0001-5445-548X

REFERENCES

1 McGonagle DG, McInnes IB, Kirkham BW, *et al*. The role of IL-17A in axial spondyloarthritis and psoriatic arthritis: recent advances and controversies. *Ann Rheum Dis* 2019;78:1167–78.
2 Braun J, Baraliakos X, Deodhar A, *et al*. Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III measure 1 study. *Ann Rheum Dis* 2017;76:1070–7.
3 Braun J, Baraliakos X, Deodhar A, *et al*. Secukinumab shows sustained efficacy and low structural progression in ankylosing spondylitis: 4-year results from the measure 1 study. *Rheumatology* 2019;58:859–68.
4 Braun J, Haibel H, de Hooge M, *et al*. Spinal radiographic progression over 2 years in ankylosing spondylitis patients treated with secukinumab: a historical cohort comparison. *Arthritis Res Ther* 2019;21.

Correction: *Dual neutralisation of interleukin-17A and interleukin-17F with bimekizumab in patients with active ankylosing spondylitis: results from a 48-week phase llb, randomised, double blind, placebo-controlled, dose-ranging study*

Van der Heijde D, Gensler LS, Deodhar, *et al*. Dual neutralisation of interleukin-17A and interleukin-17F with bimekizumab in patients with active ankylosing spondylitis: results from a 48-week phase llb, randomised, double blind, placebo-controlled, dose-ranging study. *Ann Rheum Dis* 2020;79:595–604. doi: 10.1136/annrheumdis-2020-216980

The authors have been made aware that one patient initially randomised to the bimekizumab 320 mg group withdrew from the study during the dose-blind period due to an event of oral candidiasis. Therefore, the current article contains an error in the Safety section of the Results and Discussion section:

In both instances, the statements regarding the lack of study withdrawals/discontinuations due to oral candidiasis are incorrect, as one patient withdrew from the study due to oral candidiasis.

The correct text should state:

Safety section of the Results

Oral candidiasis was reported by 3 (4.9%) patients in the bimekizumab 320 mg group during the double-blind period (table 5) and 16/303 (5.3%) of bimekizumab-treated patients in total. All cases were mild to moderate, none were serious, and resolved with systemic or topical antifungal treatment. One patient withdrew from the study during the dose-blind period due to oral candidiasis.

Discussion

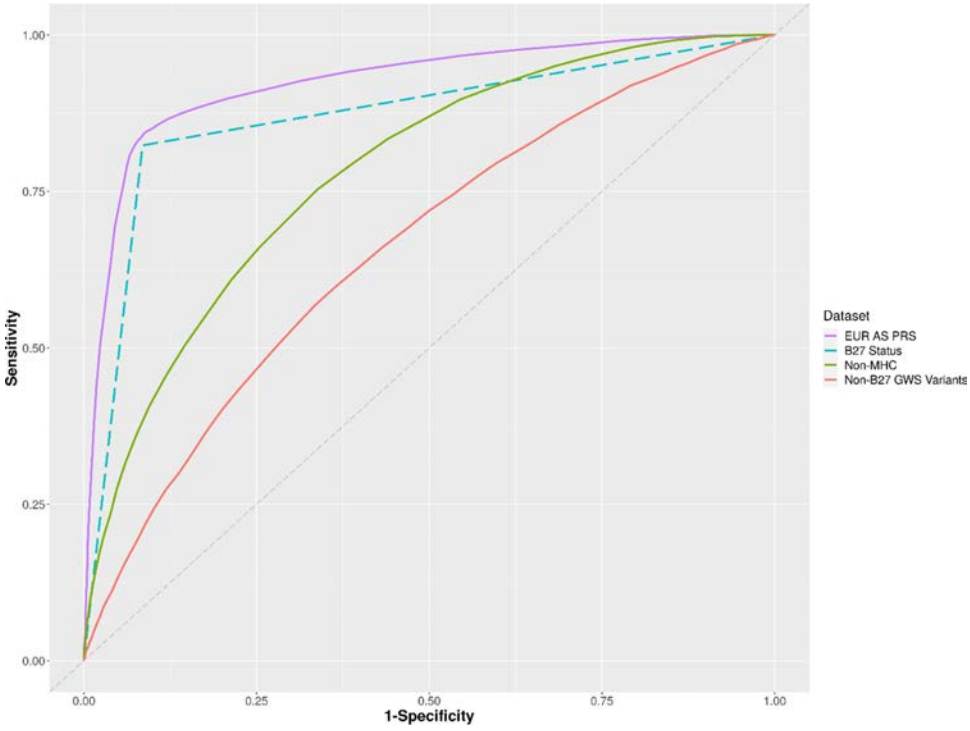
Consistent with the mechanism of action of therapies targeting the IL-17 pathway, 16 cases (5%) of oral candidiasis were reported in bimekizumab-treated patients across the 48 weeks of treatment.11 33 However, all cases were mild or moderate, and most did not lead to discontinuation.

Ann Rheum Dis 2021;**80**:e186. doi:10.1136/annrheumdis-2020-216980corr2

Correction: *Polygenic Risk Scores have high diagnostic capacity in ankylosing spondylitis*

Li Z, Wu X, Leo PJ, *et al*. Polygenic Risk Scores have high diagnostic capacity in ankylosing spondylitis. *Ann Rheum Dis* 2021;80:1168–74.

An error occurred in figure 1. The key for the figure has swapped the colours of the lines for 'B27 status' and 'non-MHC GWS variants'. The numbers for these are given in the text but the figure is wrong and should be:



Ann Rheum Dis 2021;**80**:e187. doi:10.1136/annrheumdis-2020-219446corr1