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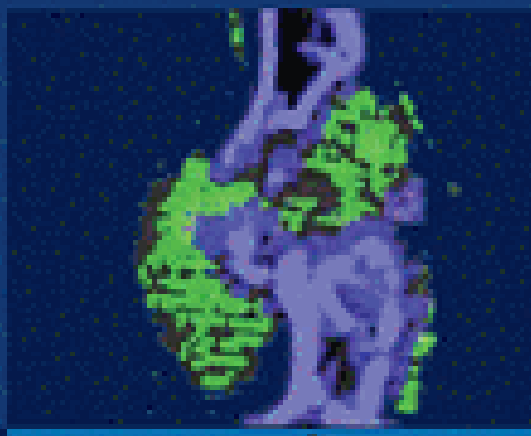

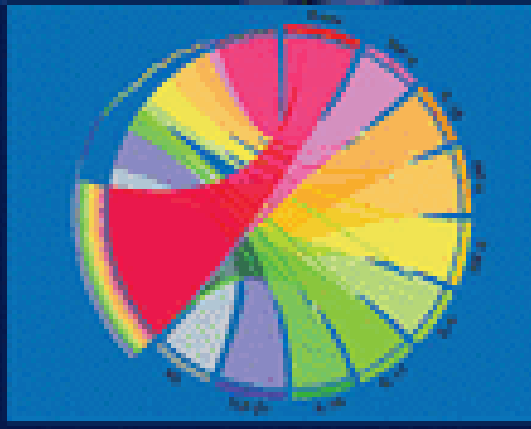

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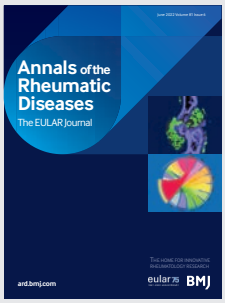

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Editorials

Heroes and pillars of rheumatology

Views on news

Recommendations

Rheumatoid arthritis

Inflammatory arthritis

Psoriatic arthritis

MORE CONTENTS ►

Electronic pages

Reflections on a contemporary European tragedy

Iain B McInnes,[1,2] Annamaria Iagnocco ,[3] Daniel Aletaha ,[4] Xenofon Baraliakos ,[5] Johannes WJ Bijlsma ,[6] Elsa F Mateus ,[7] Zoltan Szekanecz ,[8] Theodora P M Vliet Vlieland ,[9] Josef S Smolen [10]

> "No valuable talent exists without the following qualities: 1. Compassion for the oppressed; 2. Love for the good; 3. Hate against evil; 4. Courage, to express the compassion for the oppressed, the love for the good, the hate against evil loudly and unambiguously"[1]

One year ago, reflecting on the impact of COVID-19, the influenza pandemic in 1918–1920 was prominent in our thoughts noting that it cost more lives than the first World War.[2] However, the World War I was just one of the many disruptions to peace that occurred in Europe during the 20th century. Many more lives were lost in the course of the World War II; people and families were annihilated in the misguided name of a reprehensible ideology, or sacrificed by necessity to retain freedom of thought and expression!

In 2021, the shocking number of 122 300 000 victims of European violence during the 20th century was shown in an exhibition at the Jewish Museum Hohenems, a city in Vorarlberg in the federal republic of Austria. 'Numbers are mathematical objects, objects of measuring thought, but behind this number, the abstract quantity of 122 300 000, are hidden concrete characters, human lives… (The) European history of violence claimed more than 122 million lives on European soil or through the actions of European powers on non-European soil. A number that is not imaginable, not comprehensible, just abstract. From this monstrosity, this one hundred years of European history of violence, the European project of peace emerged'.[3]

We imagined a more civilised era in this new century but are sadly disappointed in the first two decades in numerous war-torn regions around the globe. Yet Europe was considered a bastion of peace, stability and prosperity. Now, moving towards the middle of 21st century (during a pandemic that has already caused ~6.5 million deaths through March),[4] we witness the instigation of a new war within our European continent, whereby an aggressive leadership sends troops to invade a neighbouring, sovereign and democratic country; where the intruder's youth is sent to kill others, and where that leadership does not hesitate to send their own youths to their deaths. People die from vicious modern weaponry; thousands are wounded; millions lose their homes and become refugees from a war imposed on them; buildings and cities are destroyed; homes, where people lived in peace, nurseries, schools, universities, libraries and hospitals transformed into rubble and ashes. For what possible ideology can such inhumanity be justified?

So please pause for a minute on the many hundred millions of people who mourned their loved ones in the 20th century—parents, wives, husbands, children, brothers, sisters, grandparents. What agonising, unfathomable aggression seeks to start wars, to kill people and to let one's own people be killed? Consider the millions of wounded persons and the devastation of homes and towns, and infrastructure that had to be rebuilt. Consider the irrevocable loss of cultural heritage. What cruelty, what barbarism! For nothing but dysfunctional ideologies! Now this, hic et nunc. Why cannot modern mankind disprove Hegel's conclusion 'that nations and governments have never learnt anything from history, or acted on any lessons they might have drawn from it'?[5]

The rheumatology community looks on in horror and weeps. Horror rendered in the cruellest contrast by our fond recollection of the VIII Ukrainian National Congress of Rheumatology, including a EULAR Cooperation with National Societies programme (EULAR ECONS), held in October 2021 in Kyiv, organised by Iuliia Biliavska and others from Volodymyr Kovalenko's Department, together with the EULAR president, Annamaria Iagnocco. Should the international rheumatology community speak of this horror? It is for politicians, political analysts and historians to make political statements. It is for international courts to make judgement on adherence or otherwise to international laws. But, we believe that medical organisations such as EULAR and medical journals such as *ARD* should demand respect of human rights. The Universal Declaration of Human Rights makes very clear statements: 'Whereas recognition of the inherent dignity and of the equal and inalienable rights of all members of the human family is the foundation of freedom, justice and peace in the world… Now, therefore, The General Assembly, proclaims this Universal Declaration of Human Rights as a common standard of achievement for all peoples and all nations, to the end that every individual and every organ of society, keeping this Declaration constantly in mind, Article 1—All human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act towards one another in a spirit of brotherhood. Article 2—Everyone is entitled to all the rights and freedoms set forth in this Declaration, without distinction of any kind,… Article 3—Everyone has the right to life, liberty and security of person.…'[6]

People suffer not only from the direct consequences of war, but also from contemporary loss of diagnostic and therapeutic opportunities and as the long-term implications of their physical and psychological privations impose later in life. Our feelings are with the Ukrainian people, with the patients and those who care and seek to care for them, now and in the times to come. Accordingly, we recognise that we as EULAR, an alliance of kindred medical, health professional and patient spirits,

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have a duty of care to support and sustain our Ukrainian colleagues now and in the times to come.

We call for an immediate ceasefire in Ukraine, for the sake of humanity, for the sake of that population and for the sake of Ukrainian patients and their healthcare providers—by corollary, we call on our Russian medical colleagues to mediate for peace.

Peace has been at the centre of the European project[3] and peace is fundamental to the remarkable achievements of humanity manifest beautifully in culture, science and modern medicine. Peace across Europe and the world is instrumental for the well-being of mankind in general, but especially for the benefit of our patients. 'Primum non nocere'…

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Greetings from the editor

Josef S Smolen

The June issue of the *Annals* always appears at the time of the Annual European Congress of Rheumatology. For the past 2 years, owing to the COVID-19 pandemic, the European Alliance of Associations for Rheumatology (EULAR) Congress was migrated to a virtual conference and it is a necessity and a pleasure to thank the whole EULAR team for the fantastic and successful efforts to run the virtual EULAR Congress smoothly, despite all the obstacles and risks of such an endeavour. However, a virtual conference is just not the same as a live meeting—a sentiment already addressed in my 2020 Greetings editorial.[1] But we all can relax a bit now: 2022 will be different from 2020 and 2021 with the opportunity to reconvene in person at the Congress in Copenhagen—what a change now in the third year of the pandemic, what a change with the availability of vaccines and medicines and the decreasing aggressiveness of the virus.

One year ago I brought the influenza pandemic in 1918–1920 to mind and mentioned that it had costed more lives than the first World War.[2] Yet now, in the middle of the pandemic that has caused already about 6.5 million deaths by end of March,[3] we have to witness the overt instigation of a new war within our peaceful European continent. Some thoughts on this tragedy and folly will be raised separately in this issue.[4] But just to clearly annotate here, as a consequence of the war in the Ukraine many patients' ailments can no longer be appropriately treated, many doctors cannot work in their hospitals and practices and medicines have become sparse. People suffer and possibly die not only from the direct consequences of war but also from the loss of diagnostic and therapeutic opportunities. For all these reasons the call for immediate resurrection of piece is of highest urgency.

Scientific advances are built on the ability to work and having necessary and sufficient resources, to do research in settings of opportunity, stability and peace. Exchange of most recent advances that arise are then reported in journals like *ARD* and at conferences like the EULAR Congress.

The possibility to report advances of rheumatology research in Europe arose exactly 75 years ago, when EULAR was founded and the First European Congress of Rheumatology was held in Copenhagen, where we meet this year to not only further advance the field but also to commemorate the foundation of EULAR. Of course, as the world's oldest rheumatology journal and as *The EULAR Journal*, *ARD* is delighted to be among the first to congratulate EULAR on the occasion of this anniversary.

To this end, *ARD*'s former editor Tore Kvien looked at some of the papers published in *ARD* in 1947 to see what has been, and what may not have been, resolved during these three quarters of a century. Among these papers were reports on the First European Congress of Rheumatology and on the latest Congress of the American Rheumatism Association, as ACR was then called—historic moments in the evolution of our field. This time-ride into the past is presented as a 'Pillar in Rheumatology' paper[5] in *ARD*'s section on 'Heroes and Pillars of Rheumatology', under which a number of highly renowned persons have been highlighted, persons of days long passed, but also persons whom many of us have still encountered and interacted with very recently.[6–11] In passing, I note that this series has raised questions around gender aspects[12] and I wish to reiterate[13] that I hope *ARD* will receive more papers on female heroes[14] in the near future. Looking back at past achievements, past achievers and previous publications are often very enlightening and important for the sake of

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advancement and to enhance scientific integrity. Confucius said: 'Study the past if you would define the future' and, in this sense, Pearl Buck reiterated: 'If you want to understand today, you have to search yesterday'.[15] To this end, Kimme Hyrich, Hans Bijlsma and Dimitris Boumpas will present to you further historic 'pillars' in the course of the second half of 2022.

Inspired by EULAR's 75th anniversary, *ARD* will host a 'EULAR News' page from now on. This will provide the leadership of EULAR with the opportunity to inform its constituency about new developments and discussions within this great organisation. *ARD* itself has founded a new section 'Images in Rheumatology'—you are welcome to read the details regarding this novel publication element in the instructions to authors which are available online. This will hopefully further increase the value of *ARD* for our readers and authors and complement the journal's scope. As you know, over and beyond this new section and the 'Heroes and Pillars' segment just mentioned above, the journal provides an opportunity to 'think the unthinkable' and to discuss 'views on news'. In this latter section of the current June issue of *ARD*, Pisetsky and Winthrop address a paper published in a non-rheumatological journal which provides new evidence on the importance of cell-mediated immunity for the protective effects of vaccines.[16] As you will certainly recall, *ARD* spearheaded the reporting on cellular immune responses in patients with rheumatic diseases, including those who lacked B cells,[17–19] and while assumed to play a major role, it was still not clear from these findings the extent to which the T-cell response is protective; some answers to this important question now come from the paper reviewed as 'News' in this issue.

What else do we present in the June issue of *ARD*? Three EULAR points to consider, or recommendations, on imaging, cardiovascular risk management and observational data are published in print this month.[20–22] Another 'Views-on-News' piece is presented by Fanouriakis *et al* and deals with new therapeutic options for systemic lupus erythematosus (SLE), including lupus nephritis,[23 24] which will likely be followed by an update of the respective EULAR recommendations in due course.

Importantly, most of the background papers on systematic reviews informing EULAR recommendations or points to consider are published in *ARD*'s sister journal *RMD Open*.[25–27] Its first editor, Bernard Combe, has been highly successful in launching the journal and has guided it thoughtfully over many years. His term as editor-in-chief will end this summer and it is a desire to thank him for his great and kind-hearted partnership over so many years. He will be succeeded by Gerd Burmester, yet another premier rheumatologist and scientist with whom the cooperation between the EULAR journals will continue at the highest level and with whom to interact will be a similar pleasure as with his predecessor. Thank you very much Bernard, and welcome Gerd!

Speaking of cooperation and recommendations: just a month ago, recommendations for the diagnosis and management of a subset of autoinflammatory diseases, jointly developed by ACR and EULAR, were published in parallel by *ARD* and *A&R*.[28 29] I am mentioning this fact to ensure that our readers realise how much collegiality and common focus toward taking the field forward govern the relationship between these two major rheumatology organisations and also the relationship between the two top rheumatology journals. Of note, the current *A&R* editor Daniel Solomon and the current *ARD* editor not only collaborate scientifically[30–33] but also cooperate in collegiality and friendship when general publication issues or matters of advancing scientific reporting arise. Indeed, spearheaded by Dr Solomon, this effort recently also involved all other EULAR and ACR journals, which published an editorial and editors' comments in parallel and, thus, in the same spirit.[34–38] Needless to say that this spirit was already present in interactions with the previous *A&R* editor, Richard Bucala, who, by the way, recently presented a fine piece on historical accounts regarding COVID-19.[39]

Suddenly, we are back to history. Admittedly, this Greetings article referred to history in several ways—to the history of infections, the history of European peace, the history of rheumatology and the history of EULAR and the importance to be willing to learn from history, for a better world, for peace and for the advancement of culture, science and health to best serve our patients…no, not just for our patients, but for all of us and the generations to come.

With my wholehearted wishes for peace and best wishes for a great EULAR Congress.

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EULAR 75-year anniversary: commentaries on key ARD papers from 1947

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EULAR is celebrating its 75-year anniversary after the foundation in 1947. ARD is contributing to this celebration by presenting a series of previously published articles that highlight the development of rheumatology over these 75 years. Comments to the first four selected papers published in 1947 appear in this issue.

Importantly, one of these papers presents a brief report from the first European congress of rheumatology, held in Copenhagen in 1947. It is, therefore, also important that the anniversary congress in 2022 is organised in the same city. The foundation of EULAR in 1947 is also described in the introduction to this report. At that time, the International League against Rheumatism (ILAR) was the global umbrella organisation and a European section was formed 'on the same lines as the Pan-American section established during the war'. Later, ILAR also included the Asian and Pacific League against Rheumatism and the African League. ILAR organised separate international congresses, the last in Edmonton in 2001, and its organisation, role and by-laws were changed around 2006. Today, each of these four 'leagues' is organising their own congress, in addition to the congress organised by the American College of Rheumatology (ACR).

The congress report illustrates that the rheumatologists also at that time had a broad focus on musculoskeletal diseases, even if some topics will not be recognised as important by younger rheumatologists today, for example, antistreptolysin antibodies. It is also mentioned that a full session addressed treatment of rheumatoid arthritis (RA) by gold salts and chemotherapy, and that 'new work reported by Svartz (Sweden) on treatment of arthritis with sulphonamides still awaits confirmation'. Professor Nanna Svartz developed sulphasalazine, which is still used in the treatment of RA and of spondyloarthritis with peripheral joint involvement.

George D. Steven published another interesting paper in 1947 with the title 'X-ray appearances in chronic rheumatism'.[1] The main focus of this paper was RA, osteoarthritis (OA) and gout. Many of the imaging findings that we also focus on today are described, like cartilage loss and bone erosions in RA. However, the opportunity for using scoring systems for evaluation of radiographic progression is not mentioned, which is perhaps not surprising since the scoring systems in RA and OA first were published in the 1971 and in 1957, respectively.[2 3]

This paper also includes a section called 'Differential Features in Other Diseases'. The first part of this section focuses on ankylosing spondylitis (AS), but very briefly. My interpretation is that AS was not recognised as an important disease to the same extent as RA, OA and gout at that time, and the description of radiographic abnormalities in AS is less detailed and accurate compared with current knowledge. Interestingly, Dr George D. Steven worked at the famous Royal National Hospital for Rheumatic Diseases in Bath, UK, which later became a leading institution for research in AS under the leadership of Andrei Calin. Some of the major advances from his research were the development of the patient-reported outcome measures Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and other important measures for this disease.[4]

Another very interesting contribution is the proceedings from the American Rheumatism Association (now called ACR) meeting in 1946. These proceedings cover more than 50 pages. Many famous rheumatologists at that time gave their presentation followed by discussion which is also included. Readers may be surprised to see that these proceedings were published in ARD and not in arthritis and rheumatology (previously arthritis and rheumatism), the official journal of ACR, but the first issue of this journal was published as late as 1958.

When reading these proceedings, it becomes very clear how rheumatology has developed during the last 75 years. Classification criteria for the various rheumatic diseases were non- existing 75 years ago, and most of the presentations were reporting case series and most of the research seemed to come from health services connected to the armed forces during and just after the second world war. Furthermore, access to therapies was poor. In his speech, the congress president, W Paul Holbrook, highlighted the need for strengthening the work in public relations and also raise awareness of rheumatic diseases among general practitioners. These topics are still very relevant today.

I was unable to find any information about rheumatoid factor, which was discovered by Erik Waaler in 1937.[5] It may have happened that this discovery had not fully disseminated to and accepted by US rheumatologists because of the war.

Philip S. Hench—the discoverer of glucocorticoids and subsequent Nobel Prize recipient—gave a talk on rheumatic diseases among American soldiers in world war II. He divided the diseases into those peculiar to war and military services and those coincidental to war and military service. In this second group, he included recurrences or exacerbations of pre-existing rheumatic diseases such as rheumatic fever, RA, fibrositis, gout, etc as well as certain diseases that had their onset while the soldier was

under no special stress, for example, RA and osteoarthritis. Gonorrhoeal arthritis was also especially mentioned. Dr. Hench also tried to make some estimates about incidences, and also about incidences related to geographic service of the soldiers.

Fibrositis was discussed in several presentations during the congress and was considered as a frequently occurring rheumatic disease.

Otto Steinbrocker, who published his famous functional classification criteria in 1949,[6] gave a presentation on painful homolateral disability of shoulder and hand with swelling and atrophy of the hand. I mention this presentation also as an example of the broad focus on various musculoskeletal diseases at the conference.

I mentioned fibrositis above. My understanding is that this term was referring to a clinical picture very similar to what we today call fibromyalgia. I also recall that fibrositis was used in Norway in the 1970s and early 1980s before the term fibromyalgia was commonly used.

In his presentation during the congress, Dr Philip Hench also briefly discussed the differentiation of psychogenic rheumatism from fibrositis. In the fourth selected paper,[7] this topic is elaborated in detail. The author, Dr. Edward W Boland, lists several disorders that are recognised as psychosomatic but states that physicians are not so familiar with the fact that disabilities of the locomotor system frequently result from psychic causes. He excludes RA as a psychosomatic disease and defines psychogenic rheumatism as the musculoskeletal expression of functional disorders, tension states or psychoneurosis. He also emphasises that the diagnosis of psychogenic rheumatism is not merely made by excluding organic disease but that positive evidence for psychoneurosis must also be established.

He also presents a comprehensive table to differentiate psychogenic rheumatism from primary fibrositis. I think it is interesting that this topic was addressed already 75 years ago, and that the debate is still ongoing regarding this topic.

In conclusion, I think these four papers, published in ARD 75 years ago, highlight the enormous development that we have faced over these years, both regarding disease classification, diagnosis and management. However, interestingly, many of the problems we still face today have already been recognised when EULAR was founded and some have remained unresolved, awaiting finalisation of pertinent research activities and therapeutic resolution. This illustrates that we should be grateful to the heroes that pioneered research and development in rheumatology. We may also be grateful to ARD for presenting all these important studies and reports and representing rheumatology research as the first ever rheumatology journal into today and to EULAR for fostering presentations and discussions of the latest advances in our field.

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Treatment of lupus: more options after a long wait

After decades of failures and setbacks, the lupus community finally had a more fruitful period marked by the successful results in two phase III and one phase II randomised controlled trials (RCTs) testing belimumab (BLM), voclosporin (VCS) and obinutuzumab (OBI), respectively, in lupus nephritis (LN), as well as of anifrolumab (ANI) in general systemic lupus erythematosus (SLE) with encouraging results in LN.[1–5] These trials overcame previous drawbacks in study design, introducing new approaches in the selection of endpoints and sample size, duration of follow-up and background treatment. The new developments provide the impetus for a critical appraisal of their place in the therapeutic armamentarium of SLE. This is highly timely, since these data were published after the 2019 updates of the EULAR and EULAR-ERA/EDTA recommendations for the management of SLE and LN, respectively.[6 7]

RECENT TRIALS IN LUPUS NEPHRITIS: KEY FINDINGS

Belimumab

Based on hints from previous trials (ie, BLISS-52 and BLISS-76) for the beneficial role of add-on BLM in renal parameters, a phase III trial, BLISS-LN, tested its efficacy in LN population (table 1).[1 8] At the end of follow-up, significantly more patients in the BLM group met the primary endpoint of renal response (43% vs 32%; OR, 1.6; 95% CI 1.0 to 2.3). Patients who received BLM also had a lower risk of renal-related events (a composite endpoint including end-stage kidney disease (ESKD); doubling of serum creatinine; increased proteinuria or impaired kidney function or kidney disease-related treatment failure) or death (HR, 0.51; 95% CI 0.34 to 0.77) while the safety profile was similar between groups.[1] Of note, the relatively high

Table 1 Designs, characteristics and outcome measures of recent randomised controlled trials in lupus nephritis

Trial	Population (n)	Design and inclusion criteria	Interventions	Follow-up	Primary endpoint and definitions	Response rates	Comments
BLISS-LN	448	► Multicentre, double-blind RCT ► eGFR >30 mL/min/1.73 m^2 ► Biopsy-proven LN (III, IV, ±V, V) ► 1:1, 50% Asian, mean eGFR: 100.5±40.2 mL/min/1.73 m^2	BLM (10 mg/kg on days 1, 15 and 29 and every 28 days)+SoC* vs Placebo +SoC	104 weeks	*Primary efficacy renal response*: 1. UPCr ≤0.7 2. eGFR ≤20% decrease from baseline or ≥60 mL/min/1.73 m^2 3. No rescue therapy	43% vs 32% (OR 1.6 95% CI, 1.0 to 2.3; p=0.03)	► Small effect size ► Sustained response ► Moderate to high GC dose (initial dose 0.5–1 mg/kg/day tapered to 10 mg/day by week 24) ► Improvement in eGFR in the BLM arm ► No safety signals
AURORA 1	357	► Multicentre, double-blind RCT ► eGFR >45 mL/min/1.73 m^2 ► Biopsy-proven LN (III, IV, ±V, V) ► 1:1, mean eGFR >90 mL/min/1.73 m^2	VCS (23.7 mg/day)+MMF (2 g/day) vs Placebo +MMF (2 g/day)	52 weeks	*Complete renal response*: 1. UPCr ≤0.5 2. eGFR ≤20% decrease from baseline or 3. ≥60 mL/min/1.73 m^2 4. No rescue therapies 5. Prednisone ≤10 mg/day	41% vs 23% (OR 2.65 95% CI, 1.64 to 4.27; p<0.0001)	► Moderate effect size ► Earlier antiproteinuric effect in VCS group ► Low initial GC dose and rapid tapering (initial dose 20–25 mg/day tapered to 2.5 mg/day by week 16)
TULIP LN	147	► Multicentre double-blind phase II RCT ► eGFR ≥35 mL/min/1.73 m^2 ► Biopsy-proven LN (III, IV±V) ► 1:1:1, mean eGFR 87.3–100.2 mL/min/1.73 m^2	Basic regimen (BR, 300 mg ANI every 4 weeks)+MMF (2 g/day) vs Intensified regimen (IR, 900 mg ANI for three doses, 300 mg thereafter)+MMF (2 g/day) vs Placebo +MMF (2 g/day)	52 weeks	Relative difference in UPCr change measured as geometric mean ratio (GMR) of the change in the combined ANI arms vs placebo	GMR vs placebo 1.031 (95% CI, 0.62 to 1.71 p=0.905) CRR (combined ANI vs placebo) 31% vs 31.1% p=0.993 (IR ANI vs placebo) 45.5% vs 31.1% p=0.162	► Better ANI exposure in the IR counterbalancing increased clearance of the drug in the BR ► Moderate GC dose (taper to ≤10 mg/day by week 12) ► Higher incidence of HZ in ANI arm
NOBILITY	125	► Multicentre, double-blind, phase II RCT ► Biopsy-proven LN (III, IV±V) ► eGFR >30 mL/min/1.73 m^2 ► 1:1, mean eGFR >100 mL/min/1.73 m^2	OBI 1 gr on day 1 and weeks 2, 24 and 26+MMF (2–2.5 g/day) vs Placebo +MMF (2–2.5 g/day)	52 weeks	*Complete renal response*: 1. UPCr<0.5 2. SCr<15% increase from baseline 3. Inactive sediment	35% vs 23% percentage difference, 12% (95% CI −3.4% to 28%; p=0.115)	► Potent depletion of B-cells in OBI arm ► Moderate GC dose (initial dose 0.5 mg/kg/day tapered to 7.5 mg/day by week 12) ► Similar safety profile in all arms

The new agents were added on standard of Care (SoC) which included glucocorticoids in variable initial doses and tapering schedules and immunosuppressive therapy (mycophenolate mofetil or iv pulse cyclophosphamide).
*SoC: GC in combination with iv CYC (500 mg every 2 weeks for 6 infusions) or MMF (3 g/day).
ANI, anifrolumab; BLM, belimumab; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; GC, glucocorticoids; GMR, geometric mean ratio; HZ, herpes zoster; LN, lupus nephritis; MMF, mycophenolate mofetil; OBI, obinutuzumab; RCT, randomised controlled trial; SCr, serum creatinine; SOC, standard of care; UPCr, urine protein–creatinine ratio; VCS, voclosporin.

glucocorticoid (GC) dose used in this trial raises the question whether lower GC doses would allow BLM to demonstrate its true efficacy. In this regard, in a *posthoc* analysis of patients who remained in the study after 24 weeks—when both mycophenolate mofetil (MMF) and GC were tapered—, patients treated with BLM had a lower risk of renal relapse (HR 0.45; 95% CI 0.28 to 0.72) and a lower rate of estimated glomerular filtration rate (eGFR) decline (eGFR slope difference 3.61; 95% CI 0.15 to 7.06), compared with placebo.[9] Based on these results, BLM in combination with standard treatment was approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), expanding its indications to include patients with LN.

Voclosporin

Following accumulating evidence in Asian patient populations pointing towards a beneficial role of calcineurin inhibitors (CNIs, mainly tacrolimus) in LN, two RCTs—phase II AURA-LV and phase III AURORA—examined the efficacy and safety of VCS in larger, multiethnic LN populations.[2 10] VCS is structurally similar to cyclosporine A (CsA), except for a molecular modification that increases its potency up to fourfold compared with CsA and leads to fast elimination of metabolites, thus drug level monitoring is not required.[11 12] In the AURORA trial, patients in the VCS group had significantly higher and earlier response rates compared with placebo (complete renal response rate at 52 weeks 41% vs 23%; OR 2.65; 95% CI 1.64 to 4.27) (table 1). Not surprisingly, this effect was mainly driven by the larger reduction in the levels of proteinuria, consistent with the antiproteinuric effect of CNIs. In January 2021, the FDA approved VCS, in combination with MMF, for the treatment of patients with LN.[13]

Obinutuzumab

Based on *posthoc* analysis of the LUNAR trial and other reports, which suggested that the degree and duration of B-cell depletion correlates with the rate of clinical response, efforts for a more potent B-cell depleting agent intensified.[14] OBI, a humanised, glycoengineered, type II anti-CD20 monoclonal antibody with greater antibody-dependent cellular cytotoxicity and direct cell death potential, compared with rituximab has been recently tested in the NOBILITY trial, a phase II RCT in 125 patients with LN, with promising results.[3 15] OBI was superior to placebo in achieving complete renal response at 52 and 104 weeks (35% vs 23%; difference 12%; 95% CI 3.4% to 28%; p=0.115, which was deemed statistically significant, and 41% vs 23%; percentage difference 19%; 95% CI 2.7% to 35%; p=0.026, respectively) without any significant safety concerns (table 1).[3]

Anifrolumab in general SLE and LN

Interferon (IFN) signalling has a key role in SLE pathogenesis. Following a successful phase II trial,[16] ANI, a human monoclonal antibody to type I IFN receptor subunit 1, was investigated in two phase III RCTs, TULIP-1 and TULIP-2 in extrarenal SLE.[4 17] TULIP-1 failed to reach its primary endpoint, the SLE Responder Index-4, but patients on ANI had better response rate in the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA). In contrast to the SLEDAI-based SRI, BICLA also captures partial responses and weights more skin compared with joint disease. In TULIP-2, more patients in the ANI group had a BICLA response compared with placebo at 52 weeks (47.8% vs 31.5%; difference 16.3%; 95% CI, 6.3 to 26.3; p=0.001). ANI showed a particular benefit in patients with predominant skin disease and enabled GC reduction. No major safety signals occurred; however, there were increased rates of herpes zoster with ANI compared with placebo (7.2% vs 1.1%, respectively).[4] All cases were cutaneous and resolved without discontinuation of therapy.

As patients with active LN were excluded from the TULIP trials, a separate phase II RCT tested the efficacy and safety of ANI (both a basic and an intensified regimen) in LN (TULIP-LN).[5] The 52-week analysis showed that the primary endpoint (relative difference in 24-hour urine protein−creatinine ratio) for the combined ANI groups vs placebo was not met (p=0.905). However, when the intensified regimen was separately compared with placebo, ANI achieved higher rates in many clinically meaningful endpoints, such as complete renal response, and GC tapering, together with improvements in extra-renal activity and serology (table 1).[5]

WHAT THERAPY, FOR WHOM AND WHEN?

All these LN trials shared a common design adding the regimens under investigation to standard of care (SoC) which includes GC/hydroxychloroquine and an immunosuppressant. While these data are encouraging, the crucial question is whether all patients with active LN should be treated with the new agents from day one of treatment.

In support of the early use of add-on treatment, investigators have argued that LN is a severe disease with significant treatment-related and disease-related morbidity, and that standard treatment leaves many patients with incomplete response, increasing their risk of progression.[18–21] Indeed, persistent proteinuria above 0.7 g/day after 1 year of treatment has been linked to adverse kidney outcomes.[22] Moreover, despite the introduction of new therapies, the risk of ESKD has remained unchanged over the last 20 years and in large clinical trials, only one in three patients reaches a complete response after 1 year of SoC treatment.[2 3 23–25] This has partly been attributed to adverse prognostic factors for kidney survival at the time of therapy initiation, such as low eGFR, nephrotic-range proteinuria, hypertension and relapsing disease in kidneys with accumulated damage.[26] Thus, advocates of early combination treatment argue that, despite the moderate additional effect, all patients should be given the benefit of newer therapies, which may also enable faster GC tapering and decrease the risk of flares and damage accrual.[27 28]

On the other hand, there are valid counterarguments against a generalised use of these drugs in all patients, as add-on to SoC from day one. Although both BLISS-LN and AURORA trials allowed the inclusion of patients with low eGFR, average eGFR in the studied populations was over 90 mL/min/1.73 m^2. Thus, the added value of the new agents in patients with high-risk features for ESKD needs further documentation. This, coupled with the modest treatment benefit from combination treatment (eg, 11% response difference between BLM and placebo) provides no definite reassurance, regarding its long-term impact on the risk of chronic kidney disease. Of note, in BLISS-LN, black patients and those treated with background cyclophosphamide (CYC) who had lower eGFR and higher baseline levels of proteinuria—traditionally considered as 'high-risk'—had no additional benefit from BLM compared with placebo although both these subgroups involved a small proportion of the study population.[1] Thus, one could argue that in patients with baseline kidney damage and impaired eGFR, add-on treatment with BLM may not be as efficacious, as such patients are more resistant to treatment.

Regarding the timing of treatment, while BLM with MMF/CYC were coadministered at the time of first diagnosis or flare in BLISS-LN, in the AURORA study more than 50% of patients were already treated with MMF at enrollment.[1 2] In a subgroup analysis, the addition of VCS was beneficial only for patients who were already on MMF at the time of study entry, implying a beneficial effect of VCS mainly on inadequately responding/refractory disease. Finally, none of the trials addressed the important question about duration of add-on therapy and its impact on the risk of relapse. This is of special interest in the case of VCS, as CNI discontinuation has long been linked to an increased relapse risk.[29]

As long-term and real-life data are eagerly awaited, identification of the patients who are more likely to benefit from combination treatment is important. Acknowledging the fact that this patient stratification may be helped in the future by the discovery of –yet undefined- biomarkers, a more clinically-based approach may offer as a good starting point. In our opinion, patients with inadequate response (after the first 3–6 months), intolerance of maximum doses of standard treatment, or at increased risk for GC-related toxicity, are the best candidates. In addition, BLM may be considered in patients with concomitant serologic activity, while patients with nephrotic range proteinuria may benefit from the potent antiproteinuric effect of VCS. Combination treatment with the new agents may also be considered from the beginning in special groups. These include younger patients—who are more likely to have severe disease and have a longer, lifelong exposure to the disease and GC, thus incurring more damage—, patients with relapsing disease—who are at risk for increased damage accrual—, patients with severe proteinuria and increased thromboembolic risk and finally patients with a pressing need for rapid GC tapering, such as those with diabetes mellitus.

In the case of ANI, it is still too early to fully assess its potential impact on LN. New data suggesting a link between pathology in the skin and the kidney, with skin disease mirroring its kidney counterpart, may imply that improvements in cutaneous disease observed with ANI could be paralleled by decreased inflammation in the kidneys.[30 31] In patients with general, extrarenal lupus, ANI could be added in patients with significant residual disease—especially skin and joints—to reach the current target of remission or low disease activity, and decrease GC use. The concern for herpes zoster infection may be alleviated with newer, inactivated vaccines, which will enable more patients with SLE to be vaccinated.

How could these data impact on the 2019 EULAR recommendations for SLE? Pending formal re-evaluation from the committee and based on drug-reimbursement policies in various countries, BLM and ANI may be added from the beginning on top of GC and hydroxychloroquine, with or without other conventional immunosuppressive drugs, or in patients unable to taper daily prednisone dose below 7.5 mg because of residual disease. In the case of LN, BLM and VCS may be used from the beginning especially in younger patients, patients with relapsing disease or marked proteinuria and, finally, patients with significant GC or disease-related damage.

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In the shadow of antibodies: how T cells defend against COVID-19

The coronaviruses are a diverse family of single-stranded RNA viruses that underlie conditions that are variably endemic, epidemic or pandemic. These conditions also differ markedly in severity. At one extreme, coronaviruses cause the common cold, an upper respiratory infection that, while symptomatic, is more bothersome than concerning. At the other extreme, SARS-CoV-2 causes a lower respiratory infection that has led to millions of deaths from devastating complications such as adult respiratory distress syndrome, cytokine storm and immunothrombosis.[1 2] In addition to its impact on individual patients, the COVID-19 pandemic has had major economic, societal and political repercussions that may persist well into the future.

The variability of coronavirus infections extends beyond the pattern and epidemiology of disease to the effects on individual patients. For COVID-19, approximately 80% or more of infected individuals will have mild-to-moderate symptoms; they can even be asymptomatic. The other patients will have severe respiratory involvement requiring hospitalisation and often have dire complications that necessitate intensive care, intubation and a wide variety of interventions that have included biologics and targeted immunosuppressives familiar to rheumatologists. Fortunately, the armamentarium of therapies continuously grows, with new antiviral agents able to attenuate infection and allow home treatment.[3 4]

The range of illnesses experienced by patients with COVID-19 is remarkable, raising important questions about the determinants of outcome. Certain facts are clear. Disease is worse in older individuals, men especially, and the presence of comorbidities such as hypertension and obesity; among other factors influencing outcomes, autoantibodies against type 1 interferons have been associated with more severe disease.[5] Unlike other infections that display a U-shaped pattern of risk by age (worse in children and older individuals), COVID-19 relatively spares children, with increasing age the dominant factor in outcome. Interestingly, in the influenza pandemic of 1918, young adults were the most seriously affected, suggesting that viruses differ in their interaction with host factors.[6 7]

As is the case in other viral infections, defence against SARS-CoV-2 involves the innate as well as adaptive immune system, B cells as well as T cells. While the cellular elements of the immune system work in concert, their roles can be distinct and also may change during the course of disease.[8–12] Elucidating the dynamics of these cell populations is important for understanding the determinants of outcome as well as for the design of strategies for treatment and prevention. Hundreds if not thousands of scientific papers have provided an extraordinary picture of the orchestration of cellular responses before, during and after infection with SARS-CoV-2.

The state of the immune system prior to infection with SARS-CoV-2 is a topic of great interest as it may have an impact on future disease course.[13–15] Indeed, as shown in a fascinating study published in *Nature* by Swadling *et al*, a population of pre-existing virus-specific T cells may be critical in the early stages of the infection, acting in some people to abort viral replication; the rapidity of the response may thereby prevent full-blown infection and even short-circuit the development of an antibody production.[16] As a result, seronegativity may represent a successful host response to infecting viruses as well as a lack of viral infection.

In their study, Swadling *et al* focused on healthcare workers (HCW) who had been intensely monitored during the first wave of the infection and were found to be negative for the virus by PCR, as well as negative for antibody by anti-spike-1 IgG, IgG and IgM antibodies to the nucleoprotein (NP), and neutralisation assays. These individuals were designated as seronegative or seronegative HCW (SN-HCW). As an explanation for seronegativity in the SN-HCW as well as their lack of virus by PCR, the study explored the possibility that these individuals had pre-existent memory T cells that, prior to the onset of antibody production, could rapidly terminate infection because of cross-reactivity to SARS-CoV-2 protein(s).

To delineate the contribution of T cells in the response of SN-HCW to the virus, the investigators analysed the responses of T cells in peripheral blood by in vitro enzyme-linked immune absorbent spot (ELISPOT) assays; for antigens, the investigators used overlapping peptides for structural proteins (spike, membrane, NP and ORF3a) as well as non-structural proteins, most importantly proteins in the replication transcription complex (RTC) that is transcribed early after infection of cells. These proteins include NSP7, SP12 and NSP13. Control populations included cohorts prior to the pandemic as well as a concurrent population that had acquired infection.

The results of the analysis were striking. Thus, despite the absence of measurable antibodies, the SN-HCW had strong responses from multispecific memory T cells; frequencies of these cells were greater than those of the unexposed, prepandemic cohort. Furthermore, the T-cell responses of the SN-HCW showed greater reactivity against the RTC antigens than the responses of matched concurrent infected individuals. Among the SN-HCW population, those with the strong T-cell responses to RTC proteins showed an increase in levels of the interferon-inducible transcript IFI27 in blood as demonstrated by PCR. As this transcript is increased with infection,[17] these results provide evidence that the SN-SWC had been infected with the virus but somehow mounted a successful antiviral defence that did not entail detectable B-cell response. Figure 1 depicts the pattern of responses of SN-HCW.

An immediate question, therefore, concerns the origin of the pre-existing T cells that can abort or terminate infection. As the authors suggest, the most likely explanation for the RTC-reactive T cells is prior infection by a coronavirus; in this scenario, the

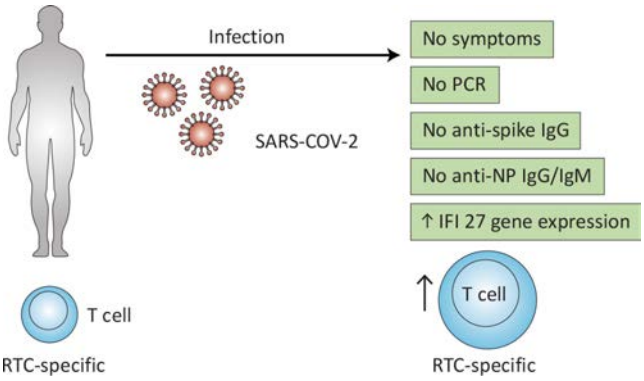

Figure 1 Immunological findings in seronegative healthcare workers (SN-HCW) following infection with SARS-CoV-2. The figure highlights the immune responses of individuals (SN-HCW) who remain seronegative following viral infection. As the figure indicates, infection leads to an increase in T cells specific for the replication transcription complex (RTC) as well as increased expression of the IFI27 gene. Other markers of infection are lacking.

non-structural proteins involved in early stages of viral replication likely show greater conservation and homology than structural proteins such as the spike protein; these proteins may, therefore, induce cross-reactive T cells more readily. As seasonal infection by coronaviruses is very common, there is abundant opportunity for the induction of a cross-reactive T-cell population that can act in infection with SARS-CoV-2 and potentially other coronaviruses. Given the frequency of coronavirus infection, it will be important to determine why memory T cells are not present more commonly in the general population although age may be a factor.[18]

Another potential setting to elucidate the interplay of B cells and T cells in defence against the virus concerns vaccination of patients who have received rituximab (RTX) to deplete CD20-positive B cells for the treatment with autoimmune and inflammatory disease. These studies have indicated that, in the absence of B cells induced by RTX treatment, antibody responses are diminished as would be expected.[19–21] The effects on T-cell responses are more complex, however, and may depend on the vaccine administered and the manner in which T-cell responses are assessed. In addition, the generation of T cells may be affected by the effects of comedication as well as underlying immunological disturbances of this patient population. Nonetheless, these studies suggest that the majority of patients who have been treated with RTX and then are vaccinated can mount measurable T-cell responses; in some patients, T-cell responses can occur even in the absence of measurable humoral responses. Studies of this kind are very relevant for rheumatologists who are concerned about the timing of vaccine administration and, ultimately, utilisation of RTX as an immunomodulatory agent.

This paper provides a rich source of data relevant to many aspects of the COVID-19 pandemic. Certainly, from the perspective of epidemiology, the results indicate that PCR and antibody assays may not invariably detect infection since, as the paper shows, infected individuals can lack these biomarkers of infection. Determining infection on the basis of T-cell reactivity, however, is inherently more complicated than assays for antibodies, requiring large peptide arrays to get adequate coverage of potential antigenic sites on any given protein. Similarly, assay for IFI27 is based on PCR determinations of peripheral blood cells, which involve additional technology.[17] Further studies will also be needed to determine the range of viral infections for which IFI27 transcripts are elevated to avoid false positive results.

The findings in this paper are also highly relevant for the design of vaccines. Current vaccines focus on structural proteins such as the spike protein and, thus, can induce antibodies to prevent viral attachment to cells for entry; the duration of antibody responses induced vaccination (as well as infection) is a potential limitation of this approach that can at least be addressed by booster injections.[22–24] Although current vaccines also induce T cells,[25 26] a vaccine targeting the RTC would involve a fundamentally different strategy; rather than blocking viral entry, the induced T cells would target infected cells, killing them before viral replication advances. As the RTC proteins are likely to be conserved, vaccines based on the induction of T cells to these proteins may have broad applicability, capable of preventing illnesses such as SARS and MERS as well as COVID-19 and whatever variants that may emerge as the pandemic evolves. Furthermore, a vaccine designed to induce T cells to the RTC could be a valuable option for patients treated with RTX, a consideration important for rheumatology as well as other subspecialties using B-cell depletion therapeutically.

The exploration of new targets of vaccines always comes with safety concerns but there are also practical aspects. Given the effectiveness of current vaccines, vaccines that target T cells would presumably be tested and ultimately deployed together with vaccines targeting the spike or other non-spike proteins. A recent study of household contacts exposed to SARS-CoV-2 showed that pre-existing cross-reactive T cells from exposure to other coronavirus were highly correlated with protection from becoming PCR positive for infection. Interestingly, in this study, non-spike protein elicited T-cell responses, further suggesting the importance of including non-spike antigens in future vaccines.[15] Demonstrating the efficacy of such vaccines may become challenging, however, as time passes and the risk of infection in the population dwindles. Investigating these issues will be an important goal for the future and can build on the seminal findings by Swadling *et al* which show why, despite the potential of SARS-CoV-2 for devastation, some infected people simply do not get sick.

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EULAR points to consider for the use of imaging to guide interventional procedures in patients with rheumatic and musculoskeletal diseases (RMDs)

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ABSTRACT

Objectives To develop evidence-based Points to Consider (PtC) for the use of imaging modalities to guide interventional procedures in patients with rheumatic and musculoskeletal diseases (RMDs).

Methods European Alliance of Associations for Rheumatology (EULAR) standardised operating procedures were followed. A systematic literature review was conducted to retrieve data on the role of imaging modalities including ultrasound (US), fluoroscopy, MRI, CT and fusion imaging to guide interventional procedures. Based on evidence and expert opinion, the task force (25 participants consisting of physicians, healthcare professionals and patients from 11 countries) developed PtC, with consensus obtained through voting. The final level of agreement was provided anonymously.

Results A total of three overarching principles and six specific PtC were formulated. The task force recommends preference of imaging over palpation to guide targeted interventional procedures at peripheral joints, periarticular musculoskeletal structures, nerves and the spine. While US is the favoured imaging technique for peripheral joints and nerves, the choice of the imaging method for the spine and sacroiliac joints has to be individualised according to the target, procedure, expertise, availability and radiation exposure. All imaging guided interventions should be performed by a trained specialist using appropriate operational procedures, settings and assistance by technical personnel.

Conclusion These are the first EULAR PtC to provide guidance on the role of imaging to guide interventional procedures in patients with RMDs.

Key messages

What is already known about this subject?

⇒ Imaging is increasingly used to guide interventional procedures in patients with rheumatic and musculoskeletal diseases (RMDs).
⇒ Imaging guided procedures require additional preparation and training as compared with palpation guided interventions.
⇒ Uncertainty persist among clinicians on which imaging technique should be used to optimally guide interventional procedures.

What does this study add?

⇒ These are the first European Alliance of Associations for Rheumatology endorsed Points to Consider (PtC) for the use of imaging to guide interventional procedures in patients with RMDs.

How might this impact on clinical practice or future developments?

⇒ These PtC give advice to clinicians in which clinical situation, for which intervention, and in which anatomical area imaging should be used to guide interventional procedures.
⇒ The research agenda highlights the gaps in evidence and areas of future studies.

INTRODUCTION

Interventional procedures such as fluid aspiration, injections and biopsies are conducted for diagnostic and therapeutic purposes in patients with different rheumatic and musculoskeletal diseases (RMDs).[1] Real-time visualisation of the needle or instruments by ultrasound (US), CT, MRI or fluoroscopy has the potential to ensure reliable placement of the needle tip/instrument in the respective anatomical area and to monitor the success of various interventions such as synovial fluid aspiration, drug injection and/or tissue biopsy.[2–6] Imaging guided procedures, however, are also more resource consuming than conventional palpation guided interventions, require additional preparation and training, and there are some studies suggesting that the outcomes of palpation and imaging guided interventions are not meaningfully different.[7 8] Clinicians are therefore still uncertain in which clinical situation, for which intervention, and in which anatomical area imaging should be used to guide interventional procedures. Advice is also needed for the setting (eg, sterility of the room, assistance by nurses) and procedural techniques (eg, direct vs indirect aspiration/injection technique).

Box 1 Preparations to conduct interventions with direct imaging guidance in situations of low (L) and high risk of infection (H)

- ⇒ Disinfection of the hands (L) or handwashing and disinfection (H).
- ⇒ Gloves (L), alternatively sterile gloves (H).
- ⇒ Sterile preparation of equipment (L, H).
- ⇒ Disinfection of the injection site (L, H).
- ⇒ For US guided interventions.
  - ⇒ Maintenance of at least 0.5 cm between the probe/gel* and the needle (L) or
  - ⇒ Extensive disinfection of the probe and use of antiseptic instead of gel (L).
  - ⇒ Sterile vinyl foil cover for the US probe and sterile gel (H).
- ⇒ Face masks† and cap (H).
- ⇒ Sterilised wraps with opening to expose the applicable site only (H).

*Use of sterile gel for ultrasound guided interventions is recommended by some national authorities.
†Obligatory for patients and healthcare provider in several countries during the COVID-19 pandemic.
L, low risk of infection; H, high risk of infection; US, ultrasound.

The broad objective of this project is to provide European Alliance of Associations for Rheumatology (EULAR) endorsed, evidence-based Points to Consider (PtC) for the use of imaging to guide interventional procedures in patients with RMDs.

METHODS

After approval by the EULAR Council, the convenors (CDejaco and XB) and the methodologist (PMM) led a task force guided by the 2014 updated EULAR standardised operating procedures (SOPs).[9] The 25 task force members consisted of rheumatologists, radiologists (all were members of the European Society of Musculoskeletal Radiology), orthopaedic surgeons, patient representatives, methodologists, a healthcare professional and two EMerging EUlar NETwork representatives from 11 countries. All members disclosed their potential conflicts of interest before the start of the process. A hygienist (which is a specialist committed to the prevention of intrahospital infections, including the prevention of surgical site infections), external to the task force, was consulted to discuss and advise the task force regarding the proposals on preparations to conduct interventions with direct imaging guidance detailed in box 1. One face-to-face and two virtual task force meetings took place, as well as interim email based feedback on the draft PtC. The second meeting was originally scheduled as a face-to-face meeting, but was then transformed into a virtual event due to the restrictions imposed by the COVID-19 pandemic.[9] Since another face-to-face meeting was recommended by EULAR SOPs in order to discuss and vote on the final PtC, a third meeting was scheduled but had ultimately to be transformed again into a webinar due to COVID-19.

At the first meeting (face-to-face), the task force agreed on three broad research questions: (1) What is the value of imaging methods (US, CT, MRI, fluoroscopy/X-ray, fusion imaging) to guide interventional procedures in patients with RMDs, (2) what is the value of different imaging settings and technical standards and (3) what is the value of different procedural techniques for imaging guided interventions.

A single systematic literature review (SLR) was conducted by two fellows (PB and FC) under the guidance of the methodologist (PMM). The convenors, together with the methodologist and fellows translated the research questions in the PICO (Population, Intervention, Comparator, Outcome) format (see online supplemental table 1).[10] The search strings were developed by an experienced librarian (LF) and applied to MEDLINE, EMBASE, the Cochrane Library and Epistemonikos databases (through 10/21). Prospective and retrospective full research articles, short reports and letters including original (patient) data, published in English and comparing different (imaging) techniques, different settings and procedural protocols to guide interventions in patients with RMDs were retrieved. Risk of bias (RoB) was assessed using the Cochrane RoB tool for randomised trials version 2 (ROB2), the RoB tool for Non-randomized Studies of Interventions and the Appraisal Tool for Cross-Sectional Studies.[11–13] The evidence summarised in the SLR was presented during the second and third task force meetings. Data were summarised in the form of tables including the RoB assessment. The SLR is published separately; however, it forms an integral and inseparable part of the present PtC manuscript and should be read as such.

At the second meeting (virtual), the task force formulated the PtC based on the evidence and expert opinion in a process of discussion and consensus. Subsequently, the draft PtC underwent structured written feedback from the task force members. At the third meeting (virtual), the PtC were refined based on the updated evidence (ie, articles published between second and third task force meeting) and feedback received, followed by voting on the PtC. Consensus was accepted if >75% of the members voted in favour of the PtC at the first round, ≥67% at the second round and at a third round >50% was accepted.[14] The Oxford centre for evidence based medicine 2011 levels of evidence (LoE) derived from the SLR were added to each PtC.[15]

Subsequently, each task force member anonymously indicated the level of agreement via Survey Monkey (LoA, 0–10 numeric rating scale ranging from 0='completely disagree' to 10='completely agree'). The mean and SD of the LoA, as well as the percentage of task force members with an agreement≥8 are presented.

Based on the gaps in the evidence and controversial points, a research agenda was formulated. The manuscript was reviewed by the EULAR Council and a revised version was finally approved by all task force members and the EULAR Council.

RESULTS

General aspects

These PtC are intended to advise qualified (physician and non-physician) healthcare professionals including rheumatologists, paediatricians, orthopaedic surgeons, neurosurgeons, radiologists, specialists in physical medicine and rehabilitation or sports medicine, general practitioners, anaesthesiologists and physical therapists on the use of imaging modalities to guide interventional procedures in patients with RMDs.

These PtC are not intended to cover all aspects of interventional procedures; we explicitly excluded interventions with the purpose of local or regional anaesthesia before surgery, interventions concerning tumours, vessels or glands as well as arthroplasty and vertebroplasty.

The task force defined 'targeted' interventions as procedures requiring a high level of precision to reach a specific anatomical area such as injection of small ganglia, cysts or tenosynovitis, aspiration of small amounts of fluid or synovial biopsy.

Table 1 EULAR Points to Consider (PtC) for the use of imaging to guide interventional procedures in patients with rheumatic and musculoskeletal diseases (RMD)

Overarching principles	LoE	LoA
A. The imaging technique should be optimised according to the procedure and the anatomical site taking into account potential side effects, radiation exposure, availability, expertise and costs.	n.a.	10.0 (0.2) 100%>8
B. Imaging guided interventional procedures should be conducted under adequate aseptic conditions (as detailed in box 1).	n.a.	10.0 (0.2) 100%>8
C. Complex imaging guided interventional procedures should be conducted with adequate assistance by technical personnel.	n.a.	9.5 (1.7) 91.7%>8
Specific Points to Consider		
1. Imaging should be preferred over palpation to guide targeted* interventional procedures at peripheral joints and periarticular structures in patients with RMDs.	3†	9.7 (0.5) 100%>8
2. Ultrasound should be used as the first imaging modality for interventional procedures at peripheral joints. Fluoroscopy may be used as an alternative.	3†	9.1 (2.1) 95.8%>8
3. Imaging should be preferred over palpation to guide targeted* injections at structures encompassing peripheral nerves. Ultrasound should be the preferred imaging modality.	3†	9.9 (0.3) 100%>8
4. Imaging should be used to guide targeted* injections at the spine.	5	9.9 (0.3) 100%>8
5. Imaging should be preferred over palpation for targeted* injections of the sacroiliac joint(s).	3†	9.9 (0.3) 100%>8
6. Healthcare professionals performing imaging guided interventional procedures must have adequate skills in the respective imaging technique and the interventional procedure.	5	8.9 (2.9) 87.5%>8

Numbers in column 'LoA' indicate the mean and SD (in parenthesis) of the LoA (range 0–10 with 0='completely disagree' to 10='completely agree'), as well as the percentage of task force members with an agreement ≥8.
*Targeted interventions are defined as procedures requiring a high level of precision to reach a specific anatomical area such as injection of small ganglia, cysts or tenosynovitis, including aspiration of small amounts of fluid or synovial biopsy.
†Levels of evidence were downgraded (from level 2 to level 3) because of bias related to randomisation, outcome assessment (trials and non-randomised studies), the population of interest (cross-sectional studies) and inadequate adjustment of potential confounders.
EULAR, European Alliance of Associations for Rheumatology; LoA, level of agreement; LoE, level of evidence; n.a., not applicable; RMDs, rheumatic and musculoskeletal diseases.

The population of interest is patients with RMDs (degenerative, inflammatory or autoimmune) including patients with painful joints, tendons, entheses and/or muscles, as well as neuropathic pain or discomfort.

These PtC may also inform patients participating in shared-decision making and healthcare provider organisations arranging care for patients with RMD.

A total of three overarching principles and six specific PtC have been formulated. They are summarised in table 1 (including the LoE and LoA) and are discussed in detail below.

Overarching principles

These refer to principles of a generic nature. They are not necessarily based on specific LoE but reflect issues of good clinical practice and the task force considered them as a framework for the subsequent, specific PtC.

A. *The imaging technique should be optimised according to the procedure and the anatomical site taking into account potential side effects, radiation exposure, availability, expertise and costs*.

The term 'technique' refers not only to the choice of the imaging device, but also to the technical procedure such as direct visualisation of the needle during the intervention as compared with indirect imaging guidance where the exact position of the target is marked first using imaging followed by blind intervention, in or out of plane needle guidance and so on, and the materials used such as different types of needles or other devices. Imaging may also support the decision of whether an intervention will be conducted by palpation or imaging guidance. A joint filled with synovial proliferation for example, might be markedly swollen but contain a small amount of fluid only. Aspiration guided by palpation might not be successful in such a situation, while imaging may help to reach the target easily. Another, less intuitive application of imaging is to confirm whether a target has been reached by an intervention guided by palpation. Evidence from the literature is absent for the majority of these aspects and the material/equipment available might differ between countries and hospitals/practices. High level of expertise for a given procedure was considered more relevant than developing a standard protocol for every possible situation, therefore, the task force made a specific PtC on skills and training below. In addition, radiation exposure should be balanced against expected accuracy and procedural safety of the intervention, and judgement may be different when the intervention is performed in young adults or children as compared with elderly people.

A related aspect is the relevance of in-of-target versus out-of-target interventions. For some indications such as injection of trigger finger, clinical studies reported no difference for whether an injection was inside or outside flexor tendon sheaths in terms of safety and clinical efficacy.[16 17] In contrast, studies on joint interventions reported higher levels of pain in case glucocorticoid injections were extra-articular as compared with intra-articular.[18 19] For epidural injection of the spine or tissue biopsy, in-target placement of the needle is mandatory in order to avoid nerve damage or to obtain a representative biopsy sample, respectively. An overview of clinical studies retrieved by the SLR comparing different procedural protocols for imaging guided interventions is depicted in table 2. Details of the studies cited are summarised in the SLR accompanying these PtC.[10]

B. *Imaging guided interventional procedures should be conducted under adequate aseptic conditions*.

While every procedure penetrating the skin of a patient must be aseptic, the level of sterility may vary. The type of intervention (eg, injection vs biopsy or direct vs indirect imaging guidance), the anatomical site (eg, enthesis vs spine) and the immunocompetency of the patient are some of the factors that may influence how 'aseptic' the setting should be.

Table 2 Overview of studies identified by the systematic literature review investigating different procedural protocols for imaging guided interventions in patients with rheumatic and musculoskeletal disease

Intervention	Comparator	Results for intervention
Intra-articular injections in sacroiliitis and ACJ arthritis[8 18 19]	Periarticular	Superior for short-term,[19] and long-term pain[18]
Shoulder joint injections in adhesive capsulitis[46 47]	SASD bursa	Superior for short-term,[47] and long-term pain.[46 47] Mixed results for efficacy
Subscapularis muscle injection in scapular pain[48]	Scapulothoracic bursa	No difference in safety and efficacy
Medial access for knee injections in OA[49 50]	Midlateral/superolateral access	No difference in safety and accuracy
US in-plane injection in knee OA[51]	US out-of-plane	No difference in accuracy, adverse events or procedural time
Bone biopsy in suspected osteomyelitis[52]	Paravertebral soft tissue	No difference in tissue acquisition
Intra-tendon sheath injection in trigger fingers[53 54]	Extra tendon sheath	No difference in safety and efficacy
Intra-epineurium injections in CTS[29]	Extra-epineurium	Superior for symptom severity and efficacy
Ulnar access for injection in CTS[55 56]	Midline/radial access	Inferior for long-term pain reduction compared with radial access[55]
Injection above the median nerve in CTS[57]	Injection under the median nerve	No difference in safety and efficacy

ACJ, acromioclavicular joint; CTS, carpal tunnel syndrome; OA, osteoarthritis; SASD, subacromial/subdeltoid; US, ultrasound.

Studies comparing different measures to guarantee the sterility of imaging guided interventional procedures are absent, and most of the studies retrieved by the SLR were relatively vague in the description of what preparations were made.[10] Based on expert opinion, and considering current clinical practice, the task force proposed preparations to conduct interventions with direct imaging guidance under aseptic conditions in relation to the presumed risk of infection (box 1). Preparation of procedures with indirect imaging guidance (ie, conduction of imaging first followed by a blind intervention) are identical to palpation guided interventions described elsewhere.[1] The suggestions in box 1 are not intended to cover every clinical situation nor to reflect all national guidelines. Some authorities for example, recommend using sterile gel for US guided interventions which is not current practice in every EULAR country.[20 21] In a severely immunocompromised patient undergoing highly invasive interventions (eg, tissue biopsy at the spine) even more intensive preparations than those listed in box 1 (such as using an operation theatre, surgical aseptic hand washing and wearing surgical gowns) may be required to minimise the risk of infection. Likewise, face masks are obligatory during the COVID-19 pandemic in many countries for patients, physicians and healthcare professionals along with a negative SARS-CoV-2 test for patients, however, it is not clear, whether face masks reduce the risk of infection in simple imaging guided interventions such as joint injections, once the pandemic is over.

C. *Complex imaging guided interventional procedures should be conducted with adequate assistance by technical personnel.*

The task force agreed that complex imaging guided procedures such as synovial tissue biopsies should be supported by technical personnel. Simple interventions such as US guided intra-articular injections could, at least in theory, be managed without assistance even though the experts were of the opinion that every imaging guided intervention benefit from assistance, particularly to maintain sterility of the setting and to ensure a high accuracy of the procedure. Technical personnel are also required to prepare equipment and drugs, to assist the procedure and to help monitoring of patients' clinical status during and after the procedure, when needed. Literature is scarce about the possible benefit of technical assistance for the prevention of adverse events as well as for cost-effectiveness; these issues should be clarified by future studies.

Specific PtC

Point to Consider 1

Imaging should be preferred over palpation to guide targeted interventional procedures at peripheral joints and periarticular structures in patients with RMDs.

The task force recognised that not all interventions at peripheral joints and periarticular structures (which include tendons, ligaments, entheses, pulleys and bursae) require imaging guidance, that imaging is not available in every setting and/or that professionals conducting interventions may not have sufficient expertise with imaging guidance. Synovial fluid aspiration of an extensively swollen knee, non-targeted injection of a metacarpophalangeal joint in a patient with rheumatoid arthritis, injection of the subacromial bursae in a patient with rotator cuff disease, injection of a trigger finger or enthesitis at lateral epicondyle might well be guided by palpation. In contrast, targeted interventions should be conducted under imaging guidance in order to guarantee a high accuracy of the procedure. The absence of immediate access to imaging, however, should not delay an urgent diagnostic procedure such as arthrocentesis in case of suspected septic arthritis.

Evidence from clinical studies indicate a better accuracy (including correct needle placement and superiority in tissue and fluid acquisition) and safety (less procedural and postprocedural pain and discomfort) for imaging than for palpation guided interventions whereas data regarding short-term and long-term efficacy are contrasting.[10] The most important limitation of these studies, however, is that they did not detangle easy (eg, subcapsular space of a highly swollen joint) from difficult to reach targets (eg, small ganglion compressing a peripheral nerve). Accordingly, the task force had to extrapolate the evidence to conclude that imaging should be preferred when a high level of precision is needed in order to reach a specific anatomical area.

Studies on costs of imaging guided interventions at peripheral joints are available only for the USA reporting large differences of costs depending on the setting and reimbursement policies of individual insurance companies.[22–24] Whether imaging guided interventions are cost-effective in the USA and EULAR countries (eg, by preventing secondary direct and indirect costs due to higher efficacy and/or lower rate of complications) is unclear so far. This aspect has been added to the research agenda.

Point to Consider 2

Ultrasound should be used as the first imaging modality for interventional procedures at peripheral joints. Fluoroscopy may be used as an alternative.

The majority of studies at peripheral joints were available for US and fluoroscopy with comparable results concerning efficacy and accuracy.[10] While fluoroscopy is still widely used in clinical practice,[25] the task force agreed that US should be preferred over fluoroscopy if both techniques were available with similar expertise, because of the absence of radiation, the better visualisation of soft tissue and the lower resource consumption by the former, as well as the fact that US can be used as part of everyday clinical practice.[24 26] The European Union directive 2013/59/EURATOM states that if a non-radiating imaging modality is available, it should be invariably used and preferred over a modality which uses ionising radiations.[27] Fluoroscopy is a valid alternative, particularly if US is not available, for joint aspiration and intra-articular injections.[28]

Other imaging modalities to guide interventional procedures of peripheral joints such as CT, MRI or fusion imaging are still a matter of research.

Point to Consider 3

Imaging should be preferred over palpation to guide targeted injections at structures encompassing peripheral nerves. Ultrasound should be the preferred imaging modality.

The task force emphasised that imaging is particularly helpful when a specific target, for example, a cyst or ganglion compressing a peripheral nerve, should be injected. One study reported a higher efficacy of intraepineural than extraepineural injection of the median nerve in patients with carpal tunnel syndrome for symptom improvement as well as for reduction of nerve swelling.[29] It is almost impossible to safely reach such a small anatomical place without imaging, even though a comparison between imaging and palpation guidance for this intervention is still missing.

The highest number of studies, most of them with low quality, were available for the comparison between US and palpation guided injections at the carpal tunnel.[10] Some of them reported more adverse events in patients undergoing palpation guided injections (eg, hand weakness, finger numbness, skin discolouration or subcutaneous fat atrophy)[30 31] whereas others found no difference in terms of safety and efficacy.[10] The task force members recognised that most studies might have been underpowered to detect rare adverse events such as accidental nerve puncture or injury of the persistent median artery, particularly in patients with anatomical variants of the median nerve. Based on clinical experience, such adverse events can easily be avoided if imaging is used to guide the injections. A bifid median nerve is the most common anatomical variant occurring in 15%–20% of the population, 11% have a persistent median artery.[32 33]

Evidence on imaging guided injections at peripheral nerves outside the carpal tunnel is scarce and mainly derives from observational and cadaveric studies,[34–39] hence, this aspect has been included in the research agenda.

Fluoroscopy is not recommended for this indication because of the absence of data from trials and the fact that nerves cannot be visualised directly with this technique. The value of other imaging methods such as MRI, or CT with/without fusion with US to guide interventions at peripheral nerves still needs to be elucidated.

Point to Consider 4

Imaging should be used to guide targeted injections at the spine.

It is common clinical practice to use imaging for injections at the spine as demonstrated by a recent survey and according to experience of the task force members.[25] In clinical practice, the choice of the technique depends on the target (US or fluoroscopy may be adequate for injections at facet joints whereas peri-radicular and epidural injections are mostly guided by CT), disease stage (CT or fusion imaging between CT/US or MRI/US may be used in cases with advanced degenerative disease or other structural damage at the spine),[40 41] local expertise and availability. Clinical studies comparing different techniques are virtually absent; a single study compared fluoroscopy with CT to conduct biopsies in case of suspected vertebral osteomyelitis revealing a better performance of the former, given its ability to adjust the needle in a vertical plane.[42] Facet joint injections are sometimes conducted under clinical guidance,[25] the percentage of in-target administration of the drug, safety and efficacy of this approach as compared with imaging guidance, however, is probably low (even though direct evidence is missing). MRI is rarely used to guide injections at the spine and there are little data from clinical studies to support its use.[10]

Point to Consider 5

Imaging should be preferred over palpation for targeted injections of the sacroiliac joint(s).

While injections of the sacroiliac joints are sometimes guided by palpation in clinical practice, the probability to reach the joint space is less than 25%.[43] Using imaging to guide injections and other interventions such as synovial tissue biopsy increases the accuracy of the procedure dramatically. One study reported that the joint space was reached in 85% of cases if US guidance was used,[44] and others found in-target needle placement in 91% of fluoroscopy guided injections.[28] Most efficacy and safety outcomes, however, were similar, independent of whether the injection was intra-articular or periarticular.[8 18] The follow-up time as well as the power of these studies to detect clinical differences, however, were limited and might thus have underestimated the true benefit of releasing drugs inside rather than outside the joint capsule.

The choice of the most appropriate imaging modality such as US, fluoroscopy, CT and MRI for sacroiliac joint injections is determined by local expertise and availability as well as by considerations of radiation exposure. Fusion imaging between US and CT might be helpful in case bony spurs or other type of joint damage limit the anatomical passage into the joint space.[45]

Point to Consider 6

Healthcare professionals performing imaging guided interventional procedures must have adequate skills in the respective imaging technique and the interventional procedure.

According to local rules and legal framework, non-physician healthcare professionals may also conduct imaging guided interventions, however, the task force strongly endorses specific training of all professionals performing these procedures. The amount of training depends on the technique and on local training requirements. EULAR has defined competencies in musculoskeletal US, and US guided interventions are part of intermediate and advanced level EULAR US courses, however, the task force considered it beyond the scope of this project to define the specific skills qualifying for imaging guided interventional procedures. Evidence from clinical studies is missing, hence this item has been added to the research agenda.

Box 2 Future research agenda

- ⇒ To compare the efficacy and accuracy of interventions guided by US, fluoroscopy, CT, MRI or fusion imaging at peripheral joints, nerves and the spine and for different indications (eg, injections, arthrocentesis or biopsy; inflammatory vs non-inflammatory conditions).
- ⇒ To compare imaging versus palpation guided interventions at different anatomical sites.
- ⇒ To compare the safety and accuracy of imaging guided interventions conducted with and without technical personnel assisting the procedure.
- ⇒ To develop and use outcome measures with importance to society including assessment of sick-leave days, cost-effectiveness and health resource consumption in studies on interventional procedures.
- ⇒ To identify and agree on outcomes measuring the success of interventional procedures (eg, amount of fluid aspiration, quality of the samples in case of biopsies, long-term pain reduction in case of injections).
- ⇒ To study the value of MRI, CT and/or fusion imaging for interventions at peripheral nerves, to study the value of US for interventions at nerves outside the carpal tunnel.
- ⇒ To study the value of imaging to avoid accidental nerve trauma as compared with palpation guided injections.
- ⇒ To investigate the effect of specific training programmes on the accuracy of imaging guided interventional procedures and to assess the learning curve of professionals conducting imaging guided interventions.
- ⇒ To define standard procedural protocols for imaging guided interventions.
- ⇒ To investigate the effect of different levels of aseptic conditions on the prevalence of infections in imaging guided interventions.
- ⇒ To evaluate the effect of echo-tip needles and needle visualisation US software for the accuracy of imaging guided interventions.
- ⇒ To compare different techniques and equipment for imaging guided interventions at different anatomical sites.

US, ultrasound.

Based on the discussions and the areas of uncertainty, a research agenda has been proposed, depicted in box 2.

DISCUSSION

These are the first EULAR PtC providing up-to-date guidance for the role of imaging to guide interventional procedures in patients with RMDs.

These principles are reflected in both the PtC and the research agenda, acknowledging also the gaps in evidence that include direct comparisons between different imaging modalities as well as the low amount of data on imaging guided interventions at peripheral nerves (particularly outside the carpal tunnel) and the spine. Besides, outcomes to measure the success of interventions (eg, amount of fluid or quality of samples in case of arthrocentesis or biopsy, respectively, reduction of damage to surrounding structures, long-term pain reduction by injections), are elusive and should be defined by future research.

Where evidence from clinical trials was controversial or absent, PtC were formulated on the basis of current clinical practice and expert opinion.[25] Good quality studies are now required to answer the numerous questions raised in the research agenda, so that future PtC can be upgraded and based on more solid evidence. The present PtC nevertheless represent a step forward in the approach to conduct interventional procedures using imaging, complementing recent EULAR recommendations for intra-articular therapies.[1] We believe that their implementation will improve patient care.

A concern is publication bias assuming that negative studies or studies demonstrating that palpation guided interventions are superior over imaging guidance were probably less frequently published. Another limitation is that the task force was mainly composed of specialists using imaging regularly, even though they also conduct palpation guided interventions routinely. Expert opinion might nevertheless be biased towards a preference of imaging over clinical guidance of interventions.

In summary, we developed three overarching principles and six specific PtC on the use of imaging for interventional procedures in RMD. These PtC are supported by evidence along with expert consensus. Unresolved issues and areas of further study have been depicted in the research agenda. We expect that much progress continues taking place in the area of imaging in RMDs, and we will carefully follow developments in the field, assuming that an amendment of these PtC may be needed within a few years.

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EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases, including systemic lupus erythematosus and antiphospholipid syndrome

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ABSTRACT

Objective To develop recommendations for cardiovascular risk (CVR) management in gout, vasculitis, systemic sclerosis (SSc), myositis, mixed connective tissue disease (MCTD), Sjögren's syndrome (SS), systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS).

Methods Following European League against Rheumatism (EULAR) standardised procedures, a multidisciplinary task force formulated recommendations for CVR prediction and management based on systematic literature reviews and expert opinion.

Results Four overarching principles emphasising the need of regular screening and management of modifiable CVR factors and patient education were endorsed. Nineteen recommendations (eleven for gout, vasculitis, SSc, MCTD, myositis, SS; eight for SLE, APS) were developed covering three topics: (1) CVR prediction tools; (2) interventions on traditional CVR factors and (3) interventions on disease-related CVR factors. Several statements relied on expert opinion because high-quality evidence was lacking. Use of generic CVR prediction tools is recommended due to lack of validated rheumatic diseases-specific tools. Diuretics should be avoided in gout and beta-blockers in SSc, and a blood pressure target <130/80 mm Hg should be considered in SLE. Lipid management should follow general population guidelines, and antiplatelet use in SLE, APS and large-vessel vasculitis should follow prior EULAR recommendations. A serum uric acid level <0.36 mmol/L (<6 mg/dL) in gout, and disease activity control and glucocorticoid dose minimisation in SLE and vasculitis, are recommended. Hydroxychloroquine is recommended in SLE because it may also reduce CVR, while no particular immunosuppressive treatment in SLE or urate-lowering therapy in gout has been associated with CVR lowering.

Conclusion These recommendations can guide clinical practice and future research for improving CVR management in rheumatic and musculoskeletal diseases.

INTRODUCTION

Patients with inflammatory rheumatic diseases have an increased risk of cardiovascular disease,[1] in comparison to the general population, which prompted the development (2010) and update (2015/16) of European League against Rheumatism (EULAR) recommendations for cardiovascular risk (CVR) management in patients with rheumatoid arthritis (RA), ankylosing spondylitis and psoriatic arthritis.[2] Accumulating evidence has shown elevated cardiovascular morbidity and mortality in other rheumatic and musculoskeletal diseases (RMDs) including gout, vasculitis, systemic sclerosis (SSc), myositis, mixed connective tissue disease (MCTD), Sjögren's syndrome (SS), systemic lupus erythematosus (SLE) and the antiphospholipid syndrome (APS).[3–13] Estimations of the incidence of cardiovascular events vary among the different disease groups (Supplementary systematic literature review (SLR) report, section II).

The higher CVR in patients with rheumatic diseases is not sufficiently explained by differences in the prevalence of traditional CVR factors,[14–18] suggesting that specific treatment recommendations tailored to patients with these conditions are needed. Chronic inflammation has been considered a key feature in cardiovascular disease pathogenesis in RMDs,[19] demonstrated also in the general population by associations with serum C-reactive protein (CRP) levels[20 21] and the efficacy of medications targeting inflammatory pathways,[22–24] while new links between inflammation, immunity and cardiometabolic factors are being researched.[25] Furthermore, patients with RMDs are often exposed to immunomodulators and glucocorticoids. Although better control of inflammation may reduce CVR in individual patients,[23 24] it is not known if some side effects of these medications might outweigh any anti-inflammatory benefit, thereby increasing the CVR.

Therefore, a EULAR Task Force was formed to develop recommendations for the management of CVR in patients with SLE, APS, gout, vasculitis, SSc, myositis, MCTD and SS based on an evidence-based approach and experts' consensus.

METHODS

Task force

Two convenors (MTN and MGT) guided the task force together with two methodologists (GJM and MMW) and four fellows (DV, GCD, EH and LB), responsible for the SLRs. Furthermore, the task force included 20 members from 11 European countries: 12 rheumatologists, 2 cardiologists, 1 metabolic medicine physician, 1 healthcare professional, 2 patient representatives and 2 EMerging EULAR NETwork members (KS and SS). The process followed the updated EULAR standardised operating procedures[26] and the Appraisal of Guidelines for Research and Evaluation II instrument.[27]

At the initial task force meeting, a first set of research questions, prepared by the convenors, was discussed with the panel and formulated on four major topics: use of cardiovascular prediction tools; interventions targeting traditional CVR factors; interventions targeting disease-related CVR factors and prevalence/incidence of cardiovascular disease. Thereafter, final research questions were developed using the PICO format (P, population; I, intervention; C, comparator; O, outcomes).

Collection of evidence

A comprehensive SLR was performed by two groups working in parallel: the gout, vasculitis, SSc/myositis/MCTD/SS group (convenor: MTN; methodologist: GJM; fellows: DV, EH and LB), and the SLE and APS group (convenor: MGT; methodologist: MMW; fellow: GCD). The protocol for the literature search was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[28] Search terms were developed with the help of experienced librarians of the VU Amsterdam, Northwest Clinics Alkmaar (for gout, vasculitis, SSc, myositis, MCTD and SS SLRs) and the National Institutes of Health, USA (for SLE and APS SLRs). PubMed, Embase and the Cochrane Library were searched for full-length English-language published articles from their inception to March 2020, while searches for incidence and prevalence of cardiovascular events were extended up to November 2020. Exclusion criteria and the search terms for each disease separately are presented in the Supplementary SLR report (section IA). The outcome was cardiovascular events rather than surrogate markers of cardiovascular disease.

Data abstraction is described in Supplementary SLR report (section IB). Retrieved studies were screened by title and abstract and articles selected for full text review were then examined independently by two persons for each group (DV, EH, LB, MN, CM, and GCD, MGT and MMW) with consultation of other task force members. A number of individually searched articles (one for gout,[29] three for SLE/APS[30–32] published after the initial search periods were included due to their importance. Data extraction was performed by the fellows (DV, EH and LB) and CM under supervision of MN and GJM in the gout, vasculitis, SSc, myositis, MCTD and SS group, and by GCD, MGT and MMW in the SLE and APS group. Quality assessment was performed using the Cochrane risk-of-bias tool[33] for randomised clinical trials and the Newcastle-Ottawa Scale[34] for observational studies. Formal pooling and meta-analysis of risks could not be performed due to the diversity of outcomes, exposures and measures of association reported in the primary studies. Evidence summaries and draft recommendations were formulated for review by all task force members before the second meeting.

Consensus on statements

The virtual second task force meeting included the presentation of SLR results and discussion and editing of the first draft of recommendations. Recommendations were accepted when ≥75% of the task force members voted agreement. After additional discussions on wording changes and voting on text, a final set of recommendations and overarching principles was prepared, including the level of evidence (LoE) and grade of recommendation (GoR) according to the Oxford Centre for Evidence Based Medicine system.[35] All task force members indicated their level of agreement (LoA) for each recommendation (0, no agreement at all; 10, full agreement), and results were averaged. The manuscript was reviewed and approved by all task force members and the EULAR Executive Committee before submission.

RESULTS

For gout, vasculitis, SSc, myositis, MCTD and SS, 105 articles were included in the SLR, while for SLE and APS, 75 articles were included (figures 1 and 2). SLR results including the flow chart and evidence tables for each PICO are presented in Supplementary SLR report (section II); all articles included in the SLRs are shown in section III.

Overarching principles

The task force developed four overarching principles emphasising the need for increased awareness of elevated CVR in RMDs, regular CVR screening, assessment and management of modifiable CVR factors, and patient education about CVR, treatment adherence and lifestyle changes (table 1).

Recommendations

Gout, vasculitis, SSc, myositis, MCTD and SS

CVR prediction tools

1. In patients with gout, vasculitis, SSc, myositis, MCTD and SS, we recommend thorough assessment of traditional CVR factors. The use of cardiovascular prediction tools as for the general population is recommended. (LoE: 5, GoR: D)

No studies have investigated the accuracy of cardiovascular prediction tools in patients with gout, vasculitis, SSc, myositis, MCTD and SS. It is currently uncertain to what extent the elevated risk for cardiovascular disease is driven by an increased prevalence of traditional or disease-specific risk factors. Existing tools, such as the Framingham Risk Score (FRS), QRISK3 or Systematic Coronary Risk Evaluation (SCORE) have been based on large general population cohorts with long follow-ups.[36–38] Therefore, for gout, vasculitis, SSc, myositis, MCTD and SS, we recommend the use of prediction tools developed in the general population.

2. For ANCA-associated vasculitis the Framingham score may underestimate the CVR. Information from the European Vasculitis Society (EUVAS) model may supplement modifiable Framingham risk factors and is recommended to take into account. (LoE: 2b, GoR: D)

In patients with ANCA-associated vasculitis the observed incidence of cardiovascular events exceeded Framingham predicted incidence in two studies.[39 40] Furthermore, one study on CVR in ANCA-associated vasculitis found a higher area under the curve (AUC) for the EUVAS model (AUC 0.73) based on age, diastolic

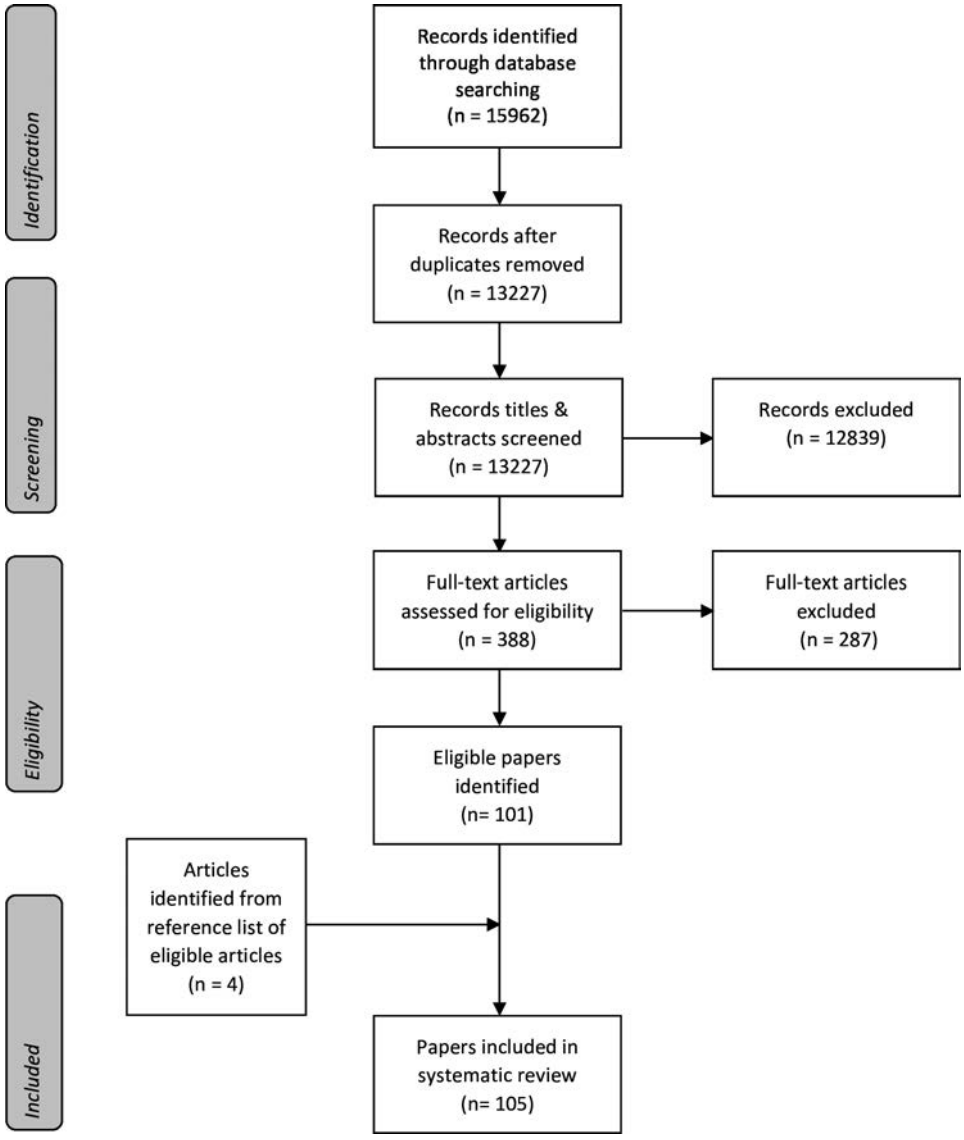

Figure 1 Flow chart of systematic literature review for cardiovascular risk management in gout, vasculitis, systemic sclerosis, myositis, mixed connective tissue disease and Sjögren's syndrome. Articles on cardiovascular incidence and prevalence are also included.

hypertension, and PR3 ANCA status in comparison with the Framingham model (AUC 0.65).[41] Although this study was not designed for the evaluation of CVR, these disease-specific factors could be used for risk assessment in addition to Framingham risk factors but further work is needed to validate these findings.

Interventions targeting traditional CVR factors

3. In patients with gout, vasculitis, SSc, myositis, MCTD, and SS, blood pressure (BP) management should follow recommendations used in the general population. (LoE: 5, GoR: D)

We found no trials that assessed the use of antihypertensive treatment in these patients. One small retrospective cohort study found an increase of severe cranial ischaemic events in patients with giant-cell arteritis (GCA) treated with beta blockers.[42] One large prospective cohort study in SSc found a protective effect of calcium channel blockers (CCB), ACE inhibitors (ACEI), and angiotensin receptor blockers (ARB) with ventricular arrhythmias.[43] Both studies did not control for confounding by indication. Altogether, currently, there is no evidence to modify the hypertension treatment target levels in patients with gout, vasculitis, SSc, myositis, MCTD and SS from those used in the general population.

4. In patients with gout, diuretics should be avoided. (LoE: 5, GoR: D)

Following the EULAR recommendations on management of gout, use of thiazide and loop diuretics should be avoided, if possible, because of their effect to increase serum uric acid (SUA) levels.[44] Instead, the use of CCB or losartan could be considered. This topic was not updated as part of this guideline as the literature search focused on the effect of antihypertensives on cardiovascular outcomes and not on potential effect on SUA levels.

5. In patients with SSc beta blockers should be avoided. (LoE: 5, GoR: D)

Although large trials are lacking and therefore based on expert opinion, beta blockers are considered contraindicated due to their effect on Raynaud's phenomenon.

6. In patients with gout, vasculitis, SSc, myositis, MCTD, and SS, lipid management should follow recommendations used in the general population. (LoE: 5, GoR: D)

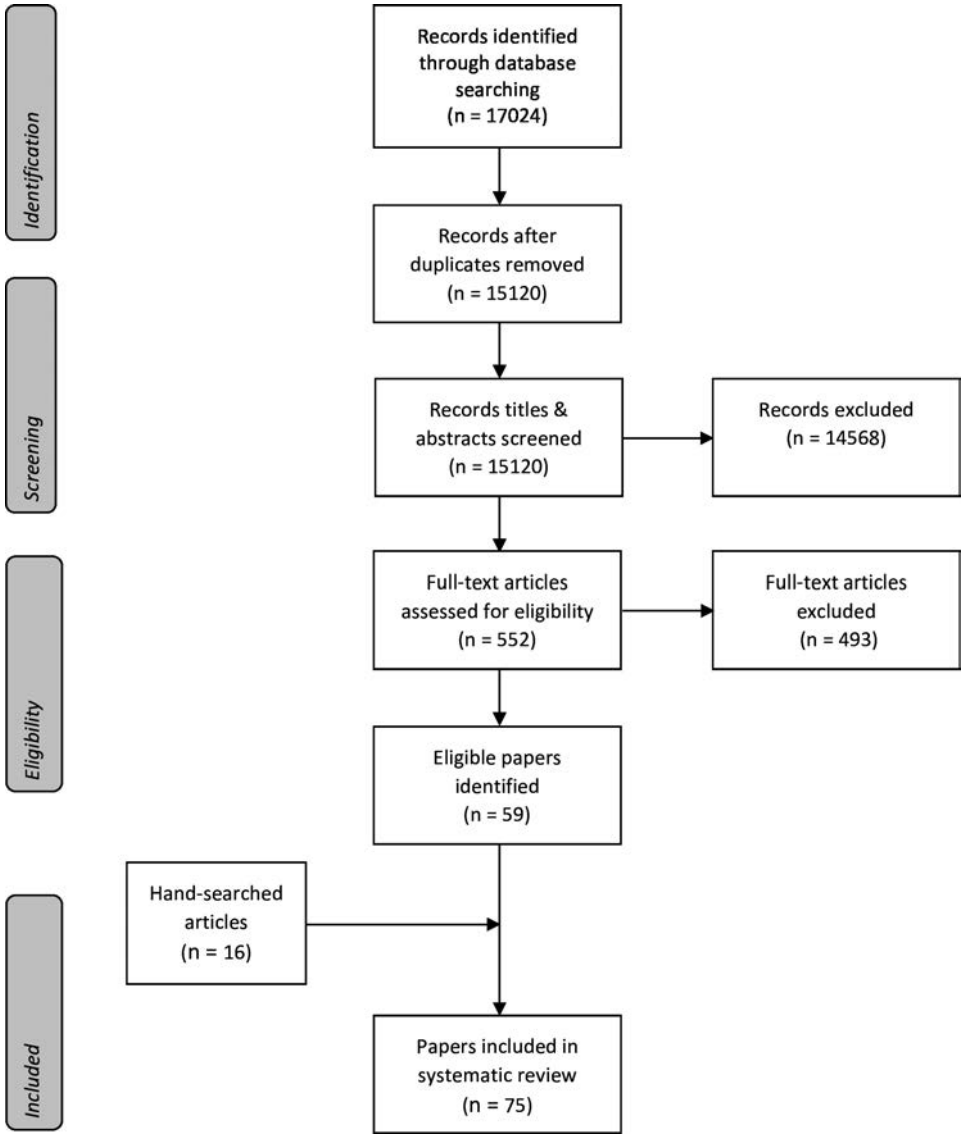

Figure 2 Flow chart of systematic literature review for cardiovascular risk management in systemic lupus erythematosus and the antiphospholipid syndrome.

In gout patients, no studies evaluated the effect of statins on cardiovascular disease or mortality in comparison with the general population. Two retrospective cohort studies suggested a protective effect of statins on mortality in patients with gout after 5 and 10 years, relative to patients not using statins.[45 46] Because of the limited evidence, we recommend following guidelines on lipid management for the general population. Furthermore, myotoxicity as side effect of the combination of a statin and prophylactic colchicine (0.5 mg/day) is rare and routine discontinuation of the statin is not recommended.[47]

Three studies in patients with GCA did not find an association between statins and cardiovascular events,[42 48 49] but a fourth study of 103 patients with GCA, 28 of whom were treated with statins, reported a lower risk of cardiovascular hospitalisations with a longer cumulative duration of statin treatment (HR 0.993 per one additional daily dose).[50] No studies controlled for confounding by indication.

7. In patients with gout, vasculitis, SSc, myositis, MCTD, and SS, standard use of low-dose aspirin for primary prevention is not recommended. Treatment with platelet inhibitors should follow recommendations used in the general population. (LoE: 2b/5, GoR: D)

In 2009 EULAR recommended the use of aspirin for prevention of cardiovascular and cerebrovascular events in individuals with large vessel vasculitis (LoE: 3, GoR: C).[51] More recently the American College of Rheumatology (ACR) has used the same literature base to conditionally recommend the use of aspirin in flow critical large vessel vasculitis.[52] However, in 2020 an update of the 2009 EULAR recommendations reappraised this evidence and concluded that the risk–benefit analysis was not favourable, and blanket use of antiplatelets was not essential unless indicated for other reasons.[53] Based on newly published studies, we agree with the 2020 iteration.[41 48 49] In patients with gout, ANCA-associated vasculitis, SSc, myositis, MCTD and SS we did not find studies on this topic.

8. In patients with gout, we recommend a SUA level below 0.36 mmol/L (6 mg/dL) to potentially lower the risk of cardiovascular events and cardiovascular mortality. (LoE: 2b, GoR: C)

Retrospective cohort studies in patients with gout showed an association between an elevated SUA (per 0.06 mmol/L (1 mg/

Table 1 EULAR overarching principles and recommendations for the management of CVR in gout, vasculitis, SSc, myositis, MCTD, SS, SLE, and APS

Overarching principles	LoA* (SD)
A. Clinicians should be aware of increased CVR in patients with RMDs including gout, vasculitis, SSc, myositis, MCTD, SS, SLE and APS. For all RMDs, reduction of disease activity is likely to lessen CVR.	9.92 (0.39)
B. Rheumatologists are responsible for CVR assessment and management in collaboration with primary care providers, internists or cardiologists and other healthcare providers.	9.55 (1.12)
C. CVR factor screening should be performed regularly in all individuals with RMDs. Risk management should include screening for and strict control of CVR factors (smoking cessation, management of blood pressure, lipids and diabetes). CVR assessment is recommended within 6 months of diagnosis and repeated based on individual patient characteristics and risk levels.	9.55 (0.84)
D. Patient education and counselling on CVR, treatment adherence and lifestyle modifications, such as healthy diet and regular physical activity, are important in the management of CVR in these patients.	9.88 (0.42)
Recommendations for gout, vasculitis, SSc, myositis, MCTD and SS	
1. In patients with gout, vasculitis, SSc, myositis, MCTD and SS, we recommend thorough assessment of traditional CVR factors. The use of cardiovascular prediction tools for the general population is recommended. (LoE: 5, GoR‡: D)	9.48 (0.84)
2. For ANCA-associated vasculitis the Framingham score may underestimate the CVR. Information from the EUVAS model may supplement modifiable Framingham risk factors and is recommended to take into account. (LoE: 2b, GoR: D)	8.59 (1.50)
3. In patients with gout, vasculitis, SSc, myositis, MCTD and SS, blood pressure management should follow recommendations used in the general population. (LoE: 5, GoR: D)	9.66 (0.62)
4. In patients with gout, diuretics should be avoided. (LoE: 5, GoR: D)	8.88 (2.06)
5. In patients with SSc beta blockers should be avoided. (LoE: 5, GoR: D)	8.92 (2.11)
6. In patients with gout, vasculitis, SSc, myositis, MCTD and SS, lipid management should follow recommendations used in the general population. (LoE: 5, GoR: D)	9.48 (1.08)
7. In patients with gout, vasculitis, SSc, myositis, MCTD and SS, standard use of platelet inhibitors for primary prevention is not recommended. Treatment with platelet inhibitors should follow recommendations used in the general population. (LoE: 2b/5, GoR: D)	9.37 (1.14)
8. In patients with gout, we recommend a serum uric acid level below 0.36 mmol/L (6 mg/dL) to potentially lower the risk on cardiovascular events and cardiovascular mortality. (LoE: 2b, GoR: C)	9.03 (1.34)
9. In patients with gout there is no preference for a particular urate-lowering therapy from the cardiovascular point of view. (LoE: 1b, GoR: B)	9.14 (1.35)
10. In patients with ANCA-associated vasculitis, remission induction and remission maintenance will also reduce CVR. (LoE: 2b, GoR: D)	9.07 (1.35)
11. In patients with giant-cell arteritis an optimal glucocorticoid regimen that balances the risk of relapse and glucocorticoid use side effects may also reduce CVR. (LoE: 2b, GoR: D)	9.14 (1.06)
Recommendations for SLE and the APS	
1. In patients with SLE and/or APS, a thorough assessment of traditional CVR factors and disease-related risk factors is recommended to guide risk factor modification. (LoE: 2b, GoR: D)	9.88 (0.32)
2A. In patients with SLE, lower levels of blood pressures are associated with lower rates of cardiovascular events and a blood pressure target of <130/80 mm Hg should be considered. (LoE: 2b, GoR: C)	9.70 (0.54)
2B. In patients with lupus nephritis, ACE inhibitors or angiotensin receptor blockers are recommended for all patients with urine protein-to-creatinine ratio >500 mg/g or arterial hypertension. (LoE: 5, GoR: D)	9.51 (0.64)
2C. In patients with APS, blood pressure management should follow recommendations used in the general population. (LoE: 5, GoR: D)	9.81 (0.39)
3. In patients with SLE and/or APS, lipid treatment should follow recommendations used in the general population. (LoE: 5, GoR: D)	9.70 (0.54)
4A. Patients with SLE may be candidates for preventative strategies as in the general population, including low-dose aspirin, based on their individual CVR profile. (LoE: 2b, GoR: D)	9.29 (1.37)
4B. In asymptomatic aPL carriers (not fulfilling any vascular or obstetric APS classification criteria) with a high-risk aPL profile with or without traditional risk factors, prophylactic treatment with low-dose aspirin (75–100 mg daily) is recommended. (LoE: 2a, GoR: B) In patients with SLE and no history of thrombosis or pregnancy complications: (1) with high-risk aPL profile, prophylactic treatment with low-dose aspirin is recommended (LoE: 2a, GoR: B); (2) with low-risk aPL profile, prophylactic treatment with low-dose aspirin may be considered. (LoE: 2b, GoR: C)	9.44 (0.97)
5. In patients with SLE, low disease activity should be maintained to also reduce CVR. (LoE: 2b, GoR: B)	9.59 (1.11)
6. In patients with SLE, treatment with the lowest possible corticosteroid dose is recommended to minimise any potential cardiovascular harm. (LoE: 2b, GoR: C)	9.59 (0.79)
7. In patients with SLE, no specific immunosuppressive medication can be recommended for the purpose of lowering the risk of cardiovascular events. (LoE: 2b, GoR: C)	9.44 (0.89)
8. In patients with SLE, treatment with hydroxychloroquine (which is recommended for all patients unless contraindicated) should be considered to also reduce the risk of cardiovascular events. (LoE: 2b, GoR: B)	9.66 (0.73)

*LoA, level of agreement; numbers in column indicate the mean (SD) of the LoA among task force members.
†LoE, level of evidence: 1a: systematic review of RCTs; 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (and low-quality RCT); 3a: systematic review of case–control studies; 3b: individual case–control study; 4: case series and poor-quality cohort and case–control studies; 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.
‡GoR, grade of recommendation: A: consistent level 1 studies; B: consistent level 2 or 3 studies, or extrapolations from level 1 studies; C: level 4 studies or extrapolations from level 2 or 3 studies; D: level 5 evidence or troublingly inconsistent or inconclusive studies of any level.
ACE, angiotensin-converting enzyme; ANCA, antineutrophil cytoplasmic antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; CVR, cardiovascular risk; EULAR, European League against Rheumatism; EUVAS, European Vasculitis Society; MCTD, mixed connective tissue disease; RMDs, rheumatic and musculoskeletal diseases; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; SSc, systemic sclerosis.

dL)) and cardiovascular events.[54 55] The association might be stronger in patients with SUA levels above 0.48 mmol/L (8 mg/dL),[56] than in patients with SUA levels higher than 0.36 mmol/L (6 mg/dL).[57] Studies on the effect of urate-lowering therapy (ULT) showed conflicting results. Evidence originates predominantly from observational studies and often lacked data on treatment adherence and SUA levels during treatment. One study showed a linear dose response relation with a decline in the CVR

in the group with the highest defined daily dose.[58] This suggests that adequate ULT possibly lowers the CVR. This possibility was supported by two studies that showed a protective association of respectively 'high dose' allopurinol and ULT resulting in SUA <0.36 mmol/L (<6 mg/dL) on cardiovascular events and cardiovascular mortality.[59 60] Altogether, although numbers of events were often low and associations were stronger for the highest SUA quartiles and higher dose ULT, it is possible that achieving lower SUA level decreases the risk on CV events. A cut-off value of 0.36 mmol/L (6 mg/dL) is used in the management of gout activity and could also benefit the risk of cardiovascular events. There is not sufficient evidence to support a threshold lower than 0.36 mmol/L (6 mg/dL) for CVR management.

9. In patients with gout there is no preference for a particular ULT from the cardiovascular point of view. (LoE: 1b, GoR: B)

Current guidelines recommend allopurinol as the first choice of ULT followed by febuxostat. Most studies on CVR compared these two xanthine oxidase inhibitors. Overall, regardless of the used dosage and duration of treatment, no difference was seen in number of cardiovascular events.[61–63] In 2018, the CARES trial reported a higher risk of cardiovascular mortality with febuxostat than allopurinol.[62] However, no difference was seen in the primary composite cardiovascular disease endpoint. Recently, the FAST trial showed no difference in CVR between patients using allopurinol or febuxostat.[29] Because of the limitations of the CARES trial (high number drop-outs, no difference in primary outcome, most events occurred after discontinuation of study) and the non-inferiority results of the FAST trial, we do not recommend the use of a specific ULT regarding cardiovascular outcomes.

Interventions targeting disease-related CVR factors

10. In patients with ANCA-associated vasculitis, remission induction and remission maintenance will also reduce CVR. (LoE: 2b, GoR: D)

In three of four included studies an association was found between high disease activity scores (Birmingham Vasculitis Activity Scores version 3) and a higher risk for cardiovascular events.[64–66]

11. In patients with GCA an optimal glucocorticoid regimen that balances the risk of relapse and glucocorticoid use side effects may be considered to also reduce CVR. (LoE: 2b, GoR: D)

In patients with vasculitis, SSc, myositis, MCTD, and SS the primary goal is disease control with the lowest possible dose of glucocorticoids. In GCA two studies found a higher CVR in patients with a higher (daily/cumulative) prednisone dose. One study found that the use of an immunosuppressant in addition to glucocorticoid was a protective factor against new cardiovascular events.[67 68] The increased CVR associated with glucocorticoids has to be balanced with the risk of relapse. Special attention and frequent evaluation of risks and benefits are warranted for patients with ongoing low dose glucocorticoids.

SLE and/or APS

CVR prediction tools

1. In patients with SLE and/or APS, a thorough assessment of traditional CVR factors and disease-related risk factors is recommended to guide risk factor modification. (LoE: 2b, GoR: D)

The FRS underestimates CVR in SLE patients[18 69–71] with stroke, more often than myocardial infarction (MI), accounting for excess 'missed' risk by the FRS.[69 70] A modified version of the FRS that used a 2.0 multiplier was found, retrospectively, to improve the measure's sensitivity from 0.13 to 0.31 while maintaining good specificity to identify patients with a moderate/high risk of coronary artery disease.[72] A study examining cardiovascular mortality in middle-aged patients with SLE found that SCORE predicted less than half the observed fatal cardiovascular events.[73] The QRISK3 tool included weights for SLE,[38] but validation studies in SLE populations have not yet been performed. Direct comparison of the performance of most commonly used generic risk assessment tools in SLE is currently lacking. A new SLE-specific risk score that included disease-related variables (SLEDAI, lupus anticoagulant and low C3) along with traditional risk factors found higher estimated risks than the American College of Cardiology/American Heart Association risk equation, except among patients whose risk was already moderate/high from traditional risk factors.[74] This prediction equation requires more testing and independent validation. Given the limitations of the current evidence, the task force did not endorse use of any particular CVR assessment tool, but instead recommended a thorough assessment of traditional and disease-related risk factors to guide cardiovascular prevention interventions.

No studies were identified that examined generic CVR prediction scores in APS. The adjusted Global APS Score (aGAPSS), a clinical score including the three major antiphospholipid antibodies (aPL), hypertension and lipidaemia, was developed to predict thrombosis, though data on cardiovascular events were not reported separately.[75] Modification of the aGAPSS by adding points for diabetes mellitus, smoking, and obesity to create a score specific for cardiovascular disease, the $aGAPSS_{CVD}$ score, increased its discriminative ability and accuracy for CVR prediction in one study,[76] but further testing is needed.

Interventions targeting traditional CVR factors

2A. In patients with SLE, lower levels of BP are associated with lower rates of cardiovascular events and a BP target of <130/80 mm Hg should be considered. (LoE: 2b, GoR: C)

2B. In patients with lupus nephritis, ACEi or ARBs are recommended for all patients with urine protein-to-creatinine ratio >500 mg/g or arterial hypertension. (LoE: 5, GoR: D)

2C. In patients with APS, hypertension management should follow recommendations used in the general population. (LoE: 5, GoR: D)

A. SLE. Hypertension is associated with a higher risk of both coronary artery disease events[77] and first ischaemic stroke[78] in SLE. It, therefore, follows that BP control with antihypertensive medications should reduce the risk of cardiovascular events.[79] Recent mean systolic BP ≥132 mm Hg was identified as a determinant of a higher risk of cardiovascular events, and systolic BP had a stronger association than diastolic BP.[80] A recent study of patients with SLE examining three BP categories (normotensive; systolic BP 130–139/diastolic BP 80–89; systolic BP ≥140/diastolic BP ≥90 mm Hg) reported an increased risk of cardiovascular events in both hypertensive groups compared with the normotensive group,[30] suggesting that a target BP of less than 130/80 should be used.

B. Lupus nephritis. Evidence specifically addressing the impact of antihypertensive treatment on cardiovascular events in lupus nephritis is scarce. In a retrospective cohort analysis,[81] risk of a cardiovascular event was not associated with treatment with ACEI/ARB, but 18% in the ACEI/ARB group had end-stage renal disease compared with 2.4% in the comparison group and this imbalance would be expected to affect the comparison of CVRs. The panel endorsed the current EULAR/ERA-EDTA

recommendation on the use of ACEI/ARB for patients with lupus nephritis with concomitant hypertension or high-level proteinuria.[32]

C. APS. No studies were identified on the use of specific antihypertensives for cardiovascular prevention in patients with APS. These patients should be managed according to recommendations for the general population.[82]

3. In patients with SLE and/or APS, hyperlipidaemia treatment should follow recommendations used in the general population. (LoE: 5, GoR: D)

Higher levels of total cholesterol and low-density lipoprotein cholesterol have been associated with a higher risk of MI and stroke in SLE.[74 78 83] One study using national administrative data found that patients with SLE treated with lipid-lowering agents had a significantly lower risk of coronary artery disease during follow-up (mean 8.4 years) than those not treated, while short-duration or long-duration statin use were both associated with a lower risk of stroke.[84] Several other observational studies included statin use as a covariate in prediction of cardiovascular events, and identified statin use as a risk factor for events, likely representing confounding by indication.[71 85–88] Diagnosis of SLE is not sufficient per se for prescribing lipid-lowering treatment for primary cardiovascular prevention.[89] In APS, no study was identified that examined the effect of lipid-lowering agents on cardiovascular events. The task force judged that hyperlipidaemia treatment should follow the recommendations used in the general population.[89]

4A. Patients with SLE may be candidates for preventive strategies as in the general population, including low-dose aspirin, based on their individual CVR profile. (LoE: 2b, GoR: D)

4B. In asymptomatic aPL carriers with a high-risk profile with or without traditional risk factors, prophylactic treatment with low-dose aspirin (75–100 mg daily) is recommended. (LoE: 2 a, GoR: B) In patients with SLE and no history of thrombosis or pregnancy complications, prophylactic treatment with low-dose aspirin is recommended for those with a high-risk aPL profile (LoE: 2a, GoR: B) and may be considered for those with a low risk APL profile. (LoE: 2b; GoR: C)

The panel agreed to include the corresponding statements (and LoE and GoR) about the prophylactic use of antiplatelets in SLE and APS from the recent EULAR recommendations for the management of SLE[90] and APS,[91] respectively. The LoA from our task force group is shown in table 1. Use of low-dose aspirin for cardiovascular prevention in patients with SLE or APS should be individualised (particularly in the presence of a high-risk aPL profile) according to EULAR recommendations.

Interventions targeting disease-related CVR factors

5. In patients with SLE, low disease activity should be maintained to also reduce CVR. (LoE: 2b, GoR: B)

SLE activity has often been reported as a predictor of cardiovascular events. With the exception of two studies,[86 92] higher time-integrated SLEDAI levels were associated with an increased risk of cardiovascular events,[69 77 79 93] more so than baseline or single measurements.[78 94 95] In three studies,[71 96 97] baseline SLEDAI was found to be higher in patients with cardiovascular events, although it was not carried to multivariable analysis. Associations of SLEDAI with cardiovascular events was found to be stronger when considering categories of activity compared with per-unit increases,[69] suggesting a non-linear association of disease activity with cardiovascular events.

Many studies did not consider simultaneously the association of measures of disease activity and SLE medication use; therefore, results may be confounded. In an analysis that adjusted for current prednisone dose, a 1-point increase in SLEDAI was marginally associated with an increased risk of cardiovascular events (relative risk 1.05, 95% CI 1.00 to 1.11).[69] Available evidence indicates that higher disease activity may be associated with a higher risk of cardiovascular events. Thus, in addition to its importance in general patient management,[90] a low-disease activity state may also have a beneficial effect on cardiovascular health.

6. In patients with SLE, treatment with the lowest possible glucocorticoid dose is recommended to minimise any potential cardiovascular harm. (LoE: 2b, GoR: C)

Mean dosage, cumulative exposure and duration of glucocorticoid treatment have all been investigated with reference to cardiovascular events in SLE. Higher current glucocorticoid dose was associated with a higher risk of atherothrombotic events, ischaemic heart disease, and/or stroke in two studies,[69 98] but was protective in one study[79] and not associated with stroke in the SLICC inception cohort.[99] Higher mean daily doses, greater cumulative doses, and ever-use of prednisone 30 mg/day or more were more consistently associated with increased risks of cardiovascular events in both cohort and case-control studies,[71 92 100 101] although glucocorticoid use was not significantly associated with cardiovascular events in two analyses of the Toronto cohort.[95 97] Not all studies adjusted for SLE activity. A retrospective study that adjusted for SLE activity[98] found that higher daily doses (prednisone >10 mg) administered continuously were significantly associated with both MI and stroke. In a retrospective and non-randomised study, patients treated at clinics following a glucocorticoid dose-minimisation strategy had lower prednisone exposures and markedly lower risks of cardiovascular damage by the SLICC measure, particularly for stroke.[102] Most evidence suggests that higher glucocorticoid exposure (cumulative and mean daily dose) increases CVR in SLE. The task force recommended treatment with the lowest possible corticosteroid dose to minimise risks of cardiovascular harm.

7. In patients with SLE, no specific immunosuppressive medication can be recommended for the purpose of lowering the risk of cardiovascular events. (LoE: 2b, GoR: C)

Use of immunosuppressants as a class in SLE have had largely null or conflicting associations with cardiovascular events.[79 99 103] Three studies from the Toronto lupus cohort reported either a protective[96] or null association,[93 97] while one study found that patients treated with immunosuppressants vs those not treated were more likely to develop a cardiovascular event in univariate but not multivariate analyses.[95] Immunosuppressive therapy was also associated to higher odds of ischaemic heart disease and cardiovascular events in the LUMINA[104] and Hopkins lupus cohort.[69]

Studies of individual medications suggest that use of methotrexate, mycophenolate, cyclosporine, or rituximab had neutral associations with cardiovascular events.[88 92 105] Conflicting results have been reported for cyclophosphamide[71 106] and azathioprine.[71 88 106]

A common limitation in many studies was the examination of ever use vs never use of immunosuppressants, which may be too crude an exposure. No studies considered issues of confounding by indication, and positive associations with cardiovascular disease may reflect risks due to associated disease activity or severity, or concomitant glucocorticoid use. Based on current evidence, the task force concluded that no specific immunosuppressive medication can be recommended for reducing the risk of cardiovascular events. Furthermore, the committee call for better quality pharmacoepidemiologic studies in future, using recent advances in this field.

8. In patients with SLE, treatment with hydroxychloroquine (which is recommended for all SLE patients, unless contraindicated) should be considered to also reduce the risk of cardiovascular events. (LoE: 2b, GoR: B)

A large body of evidence has addressed the role of antimalarials in cardiovascular prevention in SLE. In six cohort studies, antimalarial use was associated with lower risk of either atherothrombotic events or coronary artery disease,[69 77 79 88 94 107] although in one study protection was only associated with current long-term use.[69] Several other studies reported null associations.[85 87 92 93 95 103 106] Two of seven case–control studies also reported less use of hydroxychloroquine or antimalarials among cases with cardiovascular events than controls,[100 108] with only one study reporting increased risk.[97] No associations with risk of stroke specifically have been reported.[99 109] Importantly, patients with less active disease are more often treated with antimalarials, while SLE activity may be the risk factor for cardiovascular disease; this possible selection bias was not addressed. Additionally, studies did not report results stratified by the presence of APS or aPL, therefore, it is unclear if any reduced risk is limited to patients with SLE and aPL. The task force endorsed treatment with hydroxychloroquine, as should be provided to all patients with SLE, as it may also reduce the risk of cardiovascular events.

DISCUSSION

The 2021 EULAR recommendations for CVR management in RMDs comprise overarching principles and guidance informed by the currently available evidence on several potential interventions aiming to improve cardiovascular outcomes in these disorders. The LoA for most statements was high, indicating a coherent perspective on behalf of health professionals from different areas of care and patients alike for CVR reduction efforts.

The majority of the included RMDs are uncommon diseases limiting the ability to perform large observational studies to assess the impact of traditional and disease-specific risk factors on cardiovascular disease burden and clinical trials on the long-term cardiovascular effects of preventive treatments. One of the main challenges of these recommendations was the low LoE due to few studies on many of the research questions. Confounding by indication and lack of propensity adjustment was a common limitation in the included studies and therefore several statements relied on expert opinion. Future studies that better identify exposures and outcomes may help overcome these methodological issues.

There are several additional issues that need to be addressed in the future efforts for CVR management in RMDs. Systemic RMDs are complex diseases with a wide range of clinical manifestations of various severity that may affect cardiovascular health in diverse ways. Considering personalised patient care, the potential impact of individual patient clinical phenotype on cardiovascular prognosis also merits further investigation. In guidelines for cardiovascular prevention in the general population, risk stratification represents a prerequisite for CVR management (eg, BP targets or lipid-lowering therapy).[82 89] In this context, it is important to recognise that underperformance of clinical CVR prediction tools used in the general population may hamper CVR prevention and management in RMDs. The use of prediction tools that incorporate CRP[110] (eg, Reynolds risk score[111]), the presence of specific RMDs (RA, SLE) or anti-inflammatory agents (eg, QRISK3)[38] or multipliers of baseline risk (eg, modified SCORE)[112] has been suggested by some guideline committees for CVR stratification in the general population but their use in RMDs needs to be further tested and validated. Thus, studies on disease-specific tools for CVR assessment including disease-specific in addition to traditional CVR factors, as well as risk qualifiers including the evaluation of the predictive value of nonclinical tools, are warranted. These issues, along with other relevant questions such as the pragmatic use of any risk score (simplicity often aids use) will hopefully inspire future research increasing the quality of evidence in CVR management in RMDs, are presented in the Research Agenda (box 1). One of future challenges is the better identification of patient subgroups at higher CVR including for example those with longer disease duration, and number of flares/relapses (eg, in SLE, vasculitis, gout)[55 66 113–115] or those with certain demographic (age, gender, race/ethnicity)[116] and disease characteristics (eg, aPL positivity in SLE, polyarticular or tophaceous phenotype in gout).[55 113 117]

Box 1 Research agenda and future perspectives

1. Validation of existing generic and modified CVR prediction tools in large prospective studies, and development of new disease-specific equations.
2. Additive value of vascular imaging and/or circulating biomarkers in CVR assessment in RMDs.
3. Identification of patient subgroups with higher CVR.
4. Long-term effects of current and new drugs for RMDs on CVR factors and cardiovascular events.
5. Role of antithrombotic agents used in some RMDs (eg, aspirin, LMWH in SLE/APS) to reduce the overall CVR in these patients.
6. Need for large educational campaigns within the rheumatological and other medical specialties and patient associations to increase CVR awareness.
7. Best implementation methods for the CVR recommendations.

APS, antiphospholipid syndrome; CVR, cardiovascular risk; LMWH, low-molecular weight heparin; RMDs, rheumatic and musculoskeletal diseases; SLE, systemic lupus erythematosus.

Long-term effects of current and new drugs for RMDs on CVR need further investigation. The deleterious cardiometabolic effects of the excessive exposure to glucocorticoids are well known.[118] Current recommendations by the ACR[119] and the EULAR[53 90 120 121] for the management of RMDs emphasise the adverse effects and the need of the limited dose of glucocorticoids. Limiting glucocorticoid exposure to the lowest effective dose to control active disease for the shortest duration possible and eventually discontinuation, as well as weighting the benefits and risks before starting systemic glucocorticoids, can help reduce cardiovascular harm. Several anti-inflammatory agents (eg, colchicine,[122] anti-IL1b[123]) have been shown to lower cardiovascular outcomes in randomised controlled trials for secondary prevention of cardiovascular disease in the general population and other trials are ongoing (eg, hydroxychloroquine[124]) but further evidence is needed on the cardiovascular outcomes and safety of such immunoregulatory agents in RMDs. Although the role of hydroxychloroquine in APS, and of non-steroidal anti-inflammatory drugs (NSAIDs) in SLE, was examined in our SLR (Supplementary SLR report, section II), the panel agreed that any statement on the use of these medications should be deferred until more robust evidence is available. More evidence is needed about the effect of glucocorticoids, NSAIDs and IL-1 antagonists, the dosage and duration of colchicine treatment, and the risk and benefits of the concomitant use of colchicine and statins in patients with gout.

Most of the recommendations of established low-cost clinical interventions may apply to both high-resource and low-resource countries worldwide. Implementation strategies for promoting

CVR management in RMDs include interactive educational workshops involving health professionals, patients and stakeholders with the support of healthcare professional societies and patient associations, social media dissemination and strategies customised to local and national policies such as academic detailing, audits and feedback techniques.

The panel believes that these recommendations will enable healthcare providers and patients to mutually engage in a long-term care pathway tailored to patients' needs and expectations for improving cardiovascular health in RMDs. As new data accumulate, this first set of 'best available' evidence on cardiovascular prevention in gout, vasculitis, SSc, myositis, MCTD, SS, SLE and APS will be timely updated.

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EULAR points to consider when analysing and reporting comparative effectiveness research using observational data in rheumatology

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ABSTRACT

Background Comparing treatment effectiveness over time in observational settings is hampered by several major threats, among them confounding and attrition bias.

Objectives To develop European Alliance of Associations for Rheumatology (EULAR) points to consider (PtC) when analysing and reporting comparative effectiveness research using observational data in rheumatology.

Methods The PtC were developed using a three-step process according to the EULAR Standard Operating Procedures. Based on a systematic review of methods currently used in comparative effectiveness studies, the PtC were formulated through two in-person meetings of a multidisciplinary task force and a two-round online Delphi, using expert opinion and a simulation study. Finally, feedback from a larger audience was used to refine the PtC. Mean levels of agreement among the task force were calculated.

Results Three overarching principles and 10 PtC were formulated, addressing, in particular, potential biases relating to attrition or confounding by indication. Building on Strengthening the Reporting of Observational Studies in Epidemiology guidelines, these PtC insist on the definition of the baseline for analysis and treatment effectiveness. They also focus on the reasons for stopping treatment as an important consideration when assessing effectiveness. Finally, the PtC recommend providing key information on missingness patterns.

Conclusion To improve the reliability of an increasing number of real-world comparative effectiveness studies in rheumatology, special attention is required to reduce potential biases. Adherence to clear recommendations for the analysis and reporting of observational comparative effectiveness studies will improve the trustworthiness of their results.

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INTRODUCTION

Observational data are increasingly used to analyse the safety and effectiveness of new therapies in different subgroups of patients.[1] For effectiveness studies, as in randomised controlled trials (RCTs), authors typically report the proportion of patients reaching a defined clinical threshold (eg, for rheumatoid arthritis (RA): European Alliance of Associations for Rheumatology (EULAR) response rates, EULAR/American College of Rheumatology remission or low disease activity (LDA) rates) after a set time. Comparing the proportion of responders across treatments is relatively straight forward in head-to-head RCTs, since treatment groups are similar in terms of patient characteristics by means of randomisation. However, clinical trials have restrictive inclusion criteria and usually short follow-up, and thus do not provide a full picture of clinical responses for the broader patient population seen in clinical practice, especially for chronic diseases.[2] Pragmatic RCT may provide a more real-world picture of comparative effectiveness due to more liberal inclusion criteria but also have short follow-up time, at least under full randomisation.[3]

While comparative effectiveness should be assessed also in observational studies and registers, the interpretation of the results is hampered by the limitations of observational studies,[4] and in particular two potential limitations. The first limitation is related to confounding. For example, in RA registers, non-tumour necrosis factor inhibitors (TNFi) biological disease-modifying antirheumatic drugs (DMARDs) are often prescribed to older patients, with a higher burden of disease compared with patients receiving TNFi.[5 6] Assumed advantages of one of the treatments may channel patients with special characteristics, with the consequence that disease activity evolution can be incorrectly attributed to the use of the treatment. This issue is often referred to as confounding by indication or channelling bias. The second limitation is related to a specific type of selection bias called attrition bias. Attrition bias occurs when there are systematic differences between treatment groups in the number or in the way patients are lost from a study.[7] Indeed, when considering effectiveness after a certain time, it is necessary to determine how to take into account patients who stopped the treatment, for example, due to an adverse event or lack of effect, and patients lost to follow-up (eg, who stopped participating in the registry). Patients who remained on the same treatment may have a better response to the treatment, thus resulting in

a selection bias in favour of responders, yielding an overestimation of effectiveness. If there is differential attrition bias, such as more frequent treatment discontinuation of one of the treatments, or discontinuation of the treatment for different reasons, the comparative effectiveness analysis will be biased.

EULAR has previously published points to consider (PtC) on how to use observational data to analyse and report safety data in biologic registers and report clinical trial extension studies.[8 9] The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines offers a starting framework on how to report studies. With respect to biologic registers, these PtC build on the STROBE guidelines,[10] aiming to provide more detailed guidance on reporting complex exposure characteristics, such as time being exposed, drop-out and change from one exposure to another, with a clear focus on effectiveness outcomes and their analyses. There is an unmet need for PtC on the analysis of effectiveness in purely observational real-world data, especially registers, addressing three key aspects of real-world effectiveness. First, baseline of treatment is often hard to ascertain since patients start and stop different treatments over time. Thus, the 1-year follow-up of one treatment could happen 3 months after this treatment was stopped at month 9, and correspond to the start of another treatment. Second, visits often occur at variable time points. Third, treatment discontinuation is substantial and may be informative on treatment success, for instance when patients stop for ineffectiveness. A task force was created with the aim of developing EULAR PtC to analyse and report comparative effectiveness over time (eg, treatment response rate after a set time) in rheumatology.

METHODS

After approval by the EULAR Executive Committee, the convenors (DSC and AF) and the fellow (KL) convened a multidisciplinary task force to develop the PtC, guided by the consensus process outlined in the 2014 updated EULAR Standard Operating Procedures (SOPs).[7] The task force consisted of: eight rheumatologists, four epidemiologists/rheumatologists, two statisticians (DSC and TF), two patient representatives (MdW and SRS) who were also social sciences researchers, and two health professionals (TS and AS).

Two 1-day face-to-face task force meetings were held. The first meeting was convened in March 2019 to clarify the focus of the task force, identify the scope of methods considered in the systematic literature review (SLR), and determine alternative sources of information on accurate analyses to assess comparative effectiveness. The SLR was performed by the research fellow (KL), with support from two task force members (JK and SAB) and one of the convenors (DSC), to identify relevant peer-reviewed publications published in key rheumatology journal (Scientific Journal Ranking>2) in a 10-year period (between January 2008 and March 2019) and see the evolution of analysis and reporting over time. Studies without full text or with less than 100 patients were excluded. The aim was to identify studies comparing treatments on various outcomes in longitudinal observational studies of real-world patients' populations. Of the 9969 abstracts screened, 305 full-text articles were assessed for eligibility; with 211 articles included, only 35% of studies mentioned attrition, and the majority did not use a method that allows adjusting simultaneously for confounding and attrition when estimating comparative effectiveness over time (for a full description of the SLR, see[11]). During the first meeting, the task force also decided to perform a statistical simulation study to assess the accuracy of various methods found in the SLR or those suggested by task force members.

A first draft of the PtC, including 13 items, were prepared by the fellow (KL) and the two convenors (DSC and AF). The SLR and simulation results were presented to the task force at a second meeting in November 2019, where the task force formulated a set of overarching principles and consensus statements, based on the initial draft of the PtC. Consensus, defined as ≥75% of participants voting ≥8 on a 10-points scale to the inclusion of a given item, and on exact wording was undertaken through a two-round online Delphi, with the possibility to leave comments. When no consensus was reached, the statement was reformulated and submitted to a second vote. The mean and SD of the level of agreement of task force members, as well as the percentage of participants voting ≥8/10, were then calculated.

The final manuscript was reviewed and approved by all task force members and approved by the EULAR Council (formerly EULAR Executive Committee).

RESULTS

Three overarching principles (table 1) and 10 PtC (table 2) were formulated.

Overarching principles

Treatment effectiveness relates to how well a treatment performs in routine clinical settings

Although this overarching principle can easily be endorsed by everyone, it depends on how comprehensively it is defined by all stakeholders involved, including patients, and, potentially, carers (non-professional persons helping patients). It is critical that patients are involved in the selection of outcomes that should be measured because their perspective on outcomes that are important differs from those of researchers, health professionals and other stakeholders. Furthermore, how well a treatment performs is often a matter relative to other treatments, instead of an absolute assessment. In practice, there are many therapeutic options available, and the study is more useful if it contains 'all' of these, rather than just a comparison of two or three treatments. This improves the possibility to evaluate channelling and gives a more complete picture of the effectiveness relative to the options that would actually be relevant choices in practice. This is in line with the EULAR

Table 1 EULAR-endorsed overarching principles for comparative effectiveness research with observational data in rheumatology, with levels of agreement

	LoA, mean (SD)	% votes ≥8/10
A. Treatment effectiveness relates to how well a treatment performs in routine clinical settings	9.7 (1.0)	94
B. Observational data have several limitations, including confounding and missing data	9.7 (0.8)	94
C. Robust and transparent epidemiological and statistical methods increase the trustworthiness of the results from observational data	9.8 (0.4)	100

Numbers in the column 'LoA' indicate the mean and SD (in parentheses) of the LoA, as the mean agreement of the task force members on a 0–10 scale.
EULAR, European Alliance of Associations for Rheumatology; LoA, level of agreement.

Table 2 EULAR-endorsed points to consider when analysing and reporting comparative effectiveness research with observational data in rheumatology, with levels of agreement

	LoA, mean (SD)	% votes ≥8/10
1. Reporting of comparative effectiveness in observational studies must follow the STROBE guidelines	9.7 (0.7)	100
2. To provide a more complete picture of effectiveness, several outcomes across multiple health domains should be compared	9.6 (0.5)	100
3. Lost to follow-up from the study sample must be reported by the exposure of interest	9.7 (0.5)	94
4.The proportion of patients who stop and/or change therapies over time as well as the reasons for treatment discontinuation must be reported	9.7 (0.6)	94
5. Covariates should be chosen based on subject matter knowledge and model selection should be justified	9.5 (0.7)	100
6. The study baseline should be at treatment initiation and a description of how covariate measurements relate to baseline should be included	9.5 (0.5)	100
7. The analysis should be based on all patients starting a treatment and not limited to patients remaining on treatment at a certain time point	9.8 (0.4)	100
8. When treatment discontinuation occurs before the time of outcome assessment, the attrition should be taken into account in the analysis. Consider using multiple imputation techniques and/or causal inference models such as inverse probability weighting	9.3 (1.0)	100
9. Sensitivity analyses should be undertaken to explore the influence of assumptions related to missingness, particularly in case of attrition	9.6 (0.6)	100
10. Authors should prepare a statistical analysis plan in advance	9.6 (0.7)	100

Numbers in the column 'LoA' indicate the mean and SD (in parentheses) of the LoA, as the mean agreement of the task force members on a 0–10 scale.
EULAR, European Alliance of Associations for Rheumatology; LoA, level of agreement; STROBE, STrengthening the Reporting of OBservational studies in Epidemiology.

2018–2023 strategy, aiming at delivering a comprehensive quality of care framework in patients with rheumatic and musculoskeletal diseases (RMDs) (https://www.eular.org/eular_strategy_2018.cfm).

Observational studies have several limitations, including confounding and missing data

Observational studies often have longer follow-up than RCTs and represent 'real-life' patients as seen in a typical clinical practice, with multimorbidities, unscheduled changes in treatment and incomplete adherence. They are also necessary to investigate some exposures that could not, technically or ethically, be randomised. Observational studies are thus invaluable companions to RCTs. However, data can be hampered by confounding since patients are not randomised.

The main issue with missing data in observational studies is more one of quantity than of quality. Indeed, observational studies often have much more missing data than RCT, in part due to lower manpower, but also due to longer follow-up. In addition, their design as non-interventional studies mirrors clinical practice. This means patients may move to another region (and be lost for follow-up)—but they could also be lost to follow-up due to the severity of their (comorbid) disease.[12 13] Patients may decide to stop participating in the study, or they may decide to not fill in specific data. Clinicians on the other hand will also perform differently according to specific patient characteristics or routine procedures. Therefore, missing data may be sometimes missing at random, but not always.

Robust and transparent epidemiological and statistical methods increase the trustworthiness of the results

Evidence-based medicine supports clinical decision-making, allowing results to 'make sense', thereby ensuring better adherence to treatments and advice. It may also potentially improve patients' quality of life by helping them to be confident that they made the best possible choice. For complex observational studies, achieving this trustworthiness of results requires particular attention to robust, transparent and detailed methods.

Points to consider

Ptc 1: reporting of comparative effectiveness in observational studies must follow the STROBE guidelines

The STROBE guidelines already provide comprehensive reporting guidelines for observational studies.[10] However, they lack specific recommendations for longitudinal analyses.

Ptc 2: to provide a more complete picture of effectiveness, several outcomes across multiple health domains should be compared

Effectiveness is a complex construct and cannot be assessed by a single outcome. Though several studies can each look at a different outcome, a more prudent approach is to include several outcomes, across multiple health domains, to acknowledge the variety of interests of the involved stakeholders.

Ptc 3: lost to follow-up from the study sample must be reported by treatment

The following two statements aim to address potential attrition bias, by providing necessary information about the extent of lost to follow-up and the potential differential lost to follow-up. Lost to follow-up is defined as having no additional information about a patient after a given time point. In contrast, treatment discontinuation is defined as knowing that the patient stopped a specific treatment at a given time point, whether or not there is information after that time point (eg, start of a new treatment). Because treatments are often composed of several treatments, it may be necessary to be more specific when describing changes in therapies than simple start and stop of main treatment (eg, start of conventional synthetic DMARD, in addition to a biologic/targeted synthetic DMARD). It is necessary to report lost to follow-up by treatment or treatment combination, in order to provide information on potential differential loss to follow-up.

Ptc 4: the proportion of patients who stop and/or change therapies over time as well as the reasons for treatment discontinuation must be reported

Though the rate of treatment discontinuation may be similar across treatments, the reasons for this discontinuation could differ between treatments. Reasons for discontinuation have

also changed since treat-to-target approaches have become more frequent and may call for treatment tapering, especially for patients under combination therapy. For some RMDs, treatments may sometimes be discontinued when patients are in sustained clinical remission,[14 15] in other words due to effectiveness. Thus, in a worst-case scenario, one treatment could have only discontinuation for adverse events, while another could have discontinuation for remission. Consider also examining characteristics of patients who stopped or changed therapies by reason for treatment discontinuation, to determine the importance of attrition bias (eg, age, gender, and baseline disease severity for each reason of treatment discontinuation per treatment).

Ptc 5: covariates should be chosen based on subject matter knowledge and model selection should be justified

Similar to any adjustment for confounding, the list of covariates for effectiveness at a given time point should be determined based on known potential confounders. Indeed, even recent advances in model selection may still have important issues related to being too data driven,[16] including bias in variable selection, overestimation of parameters and inflated type I error.

Ptc 6: the study baseline should be at treatment initiation and a description of how covariate measurements relate to baseline should be reported

In open cohort studies, determining baseline may become quite difficult. Efforts should be made to accurately define baseline in each study, and explicitly describe whether covariates were measured at baseline. For instance, the visit to assess disease activity could have occurred 2 weeks prior to treatment initiation, while imaging data were obtained at a visit 2 months later. In addition, registers often contain several treatment courses per patients. Consider using data from all treatment courses for the same patient, applying appropriate statistical methods to take into account non-independence.

Ptc 7: the analysis should be based on all patients starting a treatment and not limited to patients remaining on treatment at a certain time point

Due to attrition, analysing only patients still on treatment at a certain time point (eg, 1 year) would lead to bias, by considering only those patients for whom the treatment did not need to be discontinued. Complete case (CC) analysis may lead to larger bias as follow-up time and thus attrition increases.

Ptc 8: when treatment discontinuation occurs before the time of outcome assessment, attrition should be taken into account in the analysis

Attrition due to treatment discontinuation is a special case of informative censoring, whereby the patients stopping treatment differ from patients remaining on treatment, for instance by having a smaller decrease in disease activity. Several analysis methods are available to correct this selection bias. However, an increase in the response rate should be interpreted carefully since an apparent increase may represent a selection of patients for whom the treatment worked well instead of an increase of treatment effectiveness over time.

In this point to consider, we encourage researchers to consider using multiple imputation techniques and/or causal inference models such as inverse probability weighting (IPW), which have been shown to be more accurate than CC analyses.[17] When data are missing at random, that is when the missingness pattern is dependent on some other variables but can be predicted from available information,[18] both methods have been shown to provide reliable estimates.[17 19 20] Nevertheless, because of the importance of model specification of missingness, some simulations studies have shown no better results from CC analyses than from multiple imputation and IPW.[21] Indeed, other studies showed better results from IPW or multiple imputations methods when the mechanism of either dropout or death were correctly specified.[22 23]

In this framework, members of the taskforce were presented a simulation study that examined the impact of specifying missingness of effectiveness outcome due to treatment discontinuation and attrition.[24 25] This study used data generated based on a collaboration of registers of biologic DMARDs including ~50 000 RA patients. The effectiveness measure assessed was LDA rate at 1 or 2 years. The methods compared included CC, Lundex,[9] IPW,[17] and a specific multiple imputation model called Confounder-Adjusted Response Rate with Attrition Correction (CARRAC). For both IPW and multiple imputations models, the covariates to specify missingness comprised reasons for treatment discontinuation, in addition to more usual patient characteristics. The conditions tested included having between 10% and 30% of patients stopping treatment or being lost to follow-up. These percentages were allowed to vary between treatment groups, to investigate differential attrition. Furthermore, a condition evaluated the impact of informative attrition, where CDAI at the time of response rate (1 year) influenced the chance of having discontinued treatment, thus making data 'not missing at random' (NMAR). Results showed that CC usually overestimated LDA at 1 year, and Lundex methods underestimated LDA at 1 year, whereas IPW and CARRAC were usually unbiased. Even though effectiveness estimates assessed by CC or Lundex methods were often quite biased for each treatment, the difference in LDA between two treatments were often closer to the true difference value.

Ptc 9: sensitivity analyses should be undertaken to explore the influence of assumptions related to missingness, particularly in case of attrition

Since assumptions and choices of covariates can have a strong impact on the estimates of effectiveness, sensitivity analyses considering different reasonable alternatives will help determine the robustness of the findings. For instance, using CC analysis assumes that the effectiveness of the treatment was similar for those who remained on treatment and for those who discontinued (eg, for lack of loss of effect). The estimate from a second analysis considering all patients who discontinued treatment as non-responders would provide the opposite viewpoint that all discontinuations are due to ineffectiveness. Thus, showing the results of both analysis gives an idea of how much effectiveness can vary based on the assumptions underlying the analyses.

Ptc 10: authors should prepare a statistical analysis plan in advance

Statistical analysis plans protect the analyses from becoming too data-driven, influenced by what is seen in the initial descriptive results. This is particularly important for observational studies since analyses are much less clear-cut than for randomised trials. Consider including details on covariates included for adjustment, how these covariates will be included in the models (eg, age as a continuous linear variable, or as a categorical factor), which outcomes will be considered, which analyses will be done, and which sensitivity analyses will be run.

DISCUSSION

Observational studies are becoming more comprehensive and detailed. Their longer follow-up allows for a better understanding of the long-term effect of treatments. However, researchers need to be mindful of the risk of biased estimations of effectiveness. Since no solution to adjust for this risk will be perfect, guidance on which information should be reported to allow a fair assessment of potential bias is critical. Indeed, these PtC expand on the STROBE guidelines regarding the importance of describing missing data patterns. Similar to STROBE guidelines, they are relevant not only to RMDs, but to most medical fields using cohort studies to assess effectiveness, and especially to chronic disease treatments.

To our knowledge, no other non-governmental organisation representing patients, healthcare professionals and scientific societies to date has developed recommendations for comparative effectiveness studies. Yet the need for guidelines becomes increasingly evident. First, evidence accrues from numerous publications in statistics, across various medical fields, focused on missing outcome data over time and how to impute them.[11–15] Overall, these studies find that missingness is often informative (ie, associated with either exposure, or the outcome that should have been measured), thereby making the data 'NMAR'. These results reinforce the message that showing missing data patterns is necessary, to inform readers about differential attrition bias, which would cause a difference in the strength of association found between treatment and the effectiveness outcome. Second, discontinuation of treatment for remission is an option, and thus previous methods such as the simple Lundex approach,[9] which considered all patients who stopped treatment as non-responder, are less appropriate than before. Though this trend may be stronger in some countries than in other, depending on local practices or recommendations, evolution in standards of care will continue, as will the need for well-documented reporting and analysing of effectiveness.

Compared with previous EULAR-endorsed PtC, Oxford Centre for Evidence-Based Medicine Levels of Evidence were omitted because no clinical studies were included. Thus, as recommended by EULAR SOP, we downgraded our recommendations to 'PtC' due to the lack of strong data-driven evidence. However, the agreement between task force members was very high. Though this taskforce represents experts from 11 countries, a limitation is that there was only one representative from Eastern Europe.

Finally, as analyses of observational data become more complex and to accommodate more intricate research questions and data collection, supporting tools should be provided to researchers. These PtC are one tool to support correct reporting of comparative effectiveness studies. Another available support is the EULAR Virtual Research Centre offering a range of resources including clinical research support. Investigators of future studies should be encouraged to implement variables to be able to adhere to these recommendations, for example, providing reasons for treatment discontinuation. R packages, SAS procedures or any other statistical software should be developed to easily implement state of the art analyses, with a detailed documentation clarifying the substantive choices that fall to the investigators.

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EULAR 2021 updated viewpoints on SARS-CoV-2 vaccination in patients with RMDs: a guidance to answer patients' questions

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The COVID-19 pandemic has significantly impacted the care and personal lives of people with rheumatic and musculoskeletal diseases (RMDs). Vaccination against COVID-19 has brought optimism and hope but has also raised questions, especially for people with inflammatory RMDs and those receiving drugs that may influence their immune system. To address these questions, EULAR has formed a Task Force of representatives of its constituents, patients, health professionals and rheumatologists experienced in the field.

This Task Force based its advice on knowledge available in November 2021, acknowledging that there is currently limited data about the performance of the different COVID-19 vaccines in patients with RMDs and in patients treated with drugs that influence the immune system. When you read this information, please bear in mind that this text will need to be updated, as new information becomes available.

Several different vaccines are used in national vaccination programmes. All of the vaccines presently being used for COVID-19 are non-live vaccines. They cannot give you the viral disease itself, nor can they transfer infection to you, or change your genetic information, nor is there any evidence that the vaccine imposes a risk to an unborn child. These vaccines have been shown to be safe in people with RMDs as well as in people receiving drugs that influence the immune system. In other infectious diseases (such as influenza), non-live vaccines have been proven to work for immune-suppressed patients. Put simply, there is no reason to withhold these vaccines from patients with RMDs and patients treated with drugs that influence the immune system.

There are a large number of vaccines under development, that work in slightly different ways. Some are being used on a large scale, these have been approved by regulatory bodies such as the World Health Organisation (WHO) and/or European Medicines Agency (EMA) or Food and Drug Administration (FDA). The use of all vaccines worldwide is regulated by local health authorities. In table 1, some more detailed info is given.

Vaccinations should ideally be given when the RMD is in a quiet phase (sometimes referred to as low disease activity or remission); it is also preferable to vaccinate before planned immunosuppression if this is being given intermittently. But of course, this is not always possible during a pandemic. Although it is suggested that vaccination is most effective when the degree of immunosuppression is low, pausing or reducing immunosuppression may increase the risk of flare, and therefore, it is generally advised not to, or only temporarily, interrupt or decrease your medication for this purpose (if you are receiving rituximab, please consult your rheumatologist).

WHEN IS VACCINATION LESS EFFECTIVE IN IMMUNOSUPPRESSED RMD PATIENTS?

The answer to this important question is based on studies that measured antibody responses to the vaccine in larger groups of RMD patients. Available data (for more details, see table 2) indicate that the immunosuppressive drugs rituximab, cyclophosphamide, mycofenolatemofetil (MMF), abatacept or prolonged use of 10 mg or more prednisone/daily may decrease the response to the vaccine. In most countries, it is therefore advised that patients using these drugs should receive a third vaccination, at least 1 month after the second vaccination, as part of the initial vaccination cycle to maximise the vaccine response.

This third injection of the vaccine, perhaps better called the third primary dose, has to be seen as part of the initial vaccination cycle. It is different from the so-called 'booster' vaccination, which confusingly, is also called a third vaccination. A booster vaccination may be intended for everyone who completed the primary vaccine series, especially since there is accumulating evidence that the immunity conferred by the vaccine may wane over time. This booster is designed to reinforce the level of immunity to the virus. Many countries have already started a booster vaccination programme. Of course, in specific cases you and your physician can make other choices, based on your personal condition and/or on the drugs you are using; if you are in doubt, consult your rheumatologist.

In addition to the COVID-19-vaccination, we highly recommend vaccination against Pneumococcus and Influenza in patients with RMDs and patients treated with drugs that affect the immune system. (For other vaccinations please consult the current EULAR recommendations on vaccinations: Furer *et al*, ARD 2020; 79: 39–52; lay version on: https://eular.org/myUploadData/files/vaccination_summary_good_for_print_final.pdf).

Frequently asked questions by patients with RMDs and patients using drugs that influence the immune system

Do I need to be vaccinated? Yes, we encourage everybody to be vaccinated against COVID-19. It

Table 1 Approved vaccinations, used in at least 5 different European countries

Type of vaccine	Pharmaceutical company	Vaccine name
Inactivated virus		
	Sinopharm	BBIBP-CorV
	Sinovac	CoronaVac
Protein / protein subunit		Not yet used
mRNA		
	Moderna	mRNA-1273
	BioNTech/Pfizer	BNT162b2
Non-replicating factor		
	Johnson&Johnson	Ad26.CoV2.s
	Oxford-Astra Zeneca	AZD1222
	Covishield (based on Oxford-AZ)	Serum Institute of India

Table 2 Immunosuppressive drugs that might influence the immune response to COVID-19 vaccinations. (See also dgrh.de/Start/Wissenschaft/Forschung/Covid-19) The advised third vaccination is part of the initial cycle of vaccination, and doesn't refer to the booster vaccination

Name of the drug	Reduced antibody response to COVID-19 vaccination; (effect on protection unknown)	Recommendation
Rituximab	Yes	third vaccination advised
Mycofenolate mofetil	Yes	third vaccination advised
prednisone	Yes, in some circumstances	When used for a prolonged period in dosage of 10 mg/day or higher: third vaccination advised
methotrexate	Possibly mild	No data available, but consider third vaccination when dosage>20 mg/week
Abatacept	Possibly yes	third vaccination advised
JAK-inhibitors (baricitinib, filgotinib, tofacitinib, upadacitinib)	Possibly yes	third vaccination advised
azathioprine	Not known	No data available, but consider third vaccination when dosage>2 mg/kg/day
Cyclophosphamide	Not known	third vaccination advised
leflunomide	Not known	No data available, but consider third vaccination when dosage>20 mg/day

NB: Current available evidence suggests that the following medications have no or little influence upon the efficacy of COVID-19 vaccination.
Conventional synthetic antirheumatic drugs: hydroxychloroquine, sulfasalazine, apremilast, tacrolimus, or lower dosages of azathioprine (2mg/kg/day or less), methotrexate (20 mg/week or less), leflunomide (20 mg/week or less) and ciclosporine (2 ½ mg/kg/day or less).
Biologicals such as the TNFalpha-blockers (adalumimab, certolizumab, etanercept, golimumab, infliximab) the inhibitors of IL-6R (sarilumab, tocilizumab), IL-17A (secukinumab, ixekizumab), IL-12/23 (ustekinumab), IL-23 (guselkumab), IL-1 (canakinumab), IL-1R (anakinra), IL-4 (dupilumab), IL-5 (mepolizumab) and anti-BLYSS (belimumab). These biologicals are more modulating than suppressing the immune system.

is widely thought that only by vaccinating we may we contain the pandemic.

Do I need to get a third (supplemental) vaccination? Based on scientific evidence a number of RMD patients will need a third vaccination as part of their initial vaccine cycle: see the list in table 2.

Do I need to get a booster vaccination? In many countries, people are now receiving booster vaccinations as part of strategies to contain the pandemic. It is advised to adhere to the national guidelines.

Is one vaccine better for me than another one? Based on available data no advice can be given for one vaccine over another for patients with RMDs. There are no large studies comparing vaccines, looking at efficacy and safety specifically in patients with RMDs. In many countries not all vaccines are available and national guidelines determine which vaccine can be given. Vaccination, using any of the available, approved vaccines, is definitely better than no vaccination.

What about vaccines that are not listed in table 1. This list is based on widely approved vaccines. For example, Sputnik V is a non-replicable vector vaccine from Gamaleya; it is approved by local health authorities of some European countries.

Can I get COVID-19 and influenza vaccinations together? Yes, they can be given together, but it is no problem when they are given at different times.

I had COVID-19 and recovered from it. Should I be vaccinated? Yes, vaccination after COVID-19 is safe and provides significant additional protection. In many countries one instead of two vaccinations are given, usually 2–6 months, after recovery from COVID-19.

Can I get the vaccination if I take antirheumatic or immunosuppressive drugs? Yes, you can. There is no danger in receiving the vaccination. The main question is whether the vaccination is effective enough. If you are using immunosuppressive drugs, please consult your rheumatologist about possible decreased efficacy (see also table 2).

Do vaccines interfere with my medication? No.

Do I need to measure my antibody response after vaccination? This is being done for research purposes in groups of patients to collect scientific data to guide clinical practice. This is not recommended in routine clinical care for individual patients, largely because it is unknown which level of antibodies predicts protection against getting infected.

Who should I consult before vaccination—my General Practitioner or my rheumatologist? GPs will be able to answer some of your questions, but for specific questions your rheumatologist should be able to help.

What data are necessary to take the right decision? Knowledge of your disease activity, drug treatment and possible comorbidities.

What about side effects? The approved, available vaccines are remarkably safe, with a similar side effect profile to the influenza vaccination. Based on the reported rare side effects, different countries use different age group rules for different vaccines. This is not related to having an RMD or not; these rules are for everybody. It is advised to adhere to the national guidelines.

What should I do in case of a flare? Luckily, the rates of flares reported in RMDs after COVID-19 vaccination is the same as the rates of flares reported in RMD patients when they are not getting vaccinated. A flare would not likely be related to the vaccine itself, but should you experience any flare for any reason, we recommend you contact your rheumatologist.

What should I do if I have side effects that last longer than 48 hours? This is unlikely, but contact your rheumatologist.

Will I need a vaccination annually as with other vaccinations for example, influenza? This is unknown for the moment, but it could very well be the case in the future.

What about long-term effects? The evidence so far suggests that, like other vaccines, COVID-19 vaccines are safe short term as well as long term. In contrast, not only can COVID-19 infection cause severe illness in the short term, but so-called 'long COVID-19' can cause severe symptoms over many months.

Am I more at risk of getting COVID-19 infection? No there is no evidence that the risk of getting the infection is higher in patients with RMDs.

Am I more at risk of getting severe COVID-19 infection? Not by your disease itself; but -like in everybody—when you have accompanying medical problems (such as chronic lung disease) or major organ damage (such as kidney problems), the risk can be higher.

Do my treatments increase the risk of severe COVID-19 infection? Most of the drugs used in RMDs have not been associated with severe infection. To date, the only treatments that have been shown to be associated with a severe COVID-19 outcome are rituximab, cyclophosphamide, MMF or using more than 10 mg glucocorticoids daily. Regarding other drugs used in RMDs, we do not have evidence that they are associated with severe COVID-19 infection. Importantly, more active disease is associated with severe outcomes related to infections, including COVID-19. In case you are using one of those drugs mentioned, talk to your rheumatologist about the best options for your situation.

Should I encourage my relatives and friends to get vaccinated? Absolutely, that's the only way to protect each other and contain the pandemic.

Am I fully protected against COVID-19 when I'm vaccinated? Unfortunately, no; you still need to adhere to the general rules: keep distance, wash your hands, ventilate rooms, avoid large groups, self-isolate if you have symptoms, etc.

Collaborators This statement was formulated by the EULAR Taskforce on COVID-19, and the EULAR Recommendations group on COVID-19. Members: Hans Bijlsma (chair), Alessia Alunno, Gerd Burmester, Roberto Caporali, Loreto Carmona, Bernard Combe, Richard Conway, Jeffrey Curtis, Ori Elkayam, Laure Gossec, Lukas Haupt, Marloes Heijstek, Annamaria Iagnocco, John Isaacs, Istvan Juhasz, Feline Kroon, Robert Landewe, Pedro Machado, Souzi Makri, Xavier Mariette, Iain McInnes, Puja Mehta, Ulf Muller-Ladner, Aurelie Najm, Victoria Navarro-Compan, Julia Rautenstrauch, Diana Rodrigues, Hendrik Schulze-Koops, Josef Smolen, Tanja Stamm, Thea Vliet Vlieland, Dieter Wiek and Kevin Winthrop.

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EPIDEMIOLOGICAL SCIENCE

Short-term, intermediate-term and long-term risks of acute coronary syndrome in cohorts of patients with RA starting biologic DMARDs: results from four Nordic countries

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ABSTRACT

Objectives To compare the 1-year, 2-year and 5-year incidences of acute coronary syndrome (ACS) in patients with rheumatoid arthritis (RA) starting any of the biologic disease-modifying antirheumatic drugs (bDMARDs) currently available in clinical practice and to anchor these results with a general population comparator.

Methods Observational cohort study, with patients from Denmark, Finland, Norway and Sweden starting a bDMARD during 2008–2017. Time to first ACS was identified through register linkages. We calculated the 1-year, 2-year and 5-year incidence rates (IR) (on drug and ever since treatment start) and used Cox regression (HRs) to compare ACS incidences across treatments taking ACS risk factors into account. Analyses were further performed separately in subgroups defined by age, number of previous bDMARDs and history of cardiovascular disease. We also compared ACS incidences to an individually matched general population cohort.

Results 24 083 patients (75% women, mean age 56 years) contributing 40 850 treatment courses were included. During the maximum (5 years) follow-up (141 257 person-years (pyrs)), 780 ACS events occurred (crude IR 5.5 per 1000 pyrs). Overall, the incidence of ACS in RA was 80% higher than that in the general population. For all bDMARDs and follow-up definitions, HRs were close to 1 (etanercept as reference) with the exception of the 5-year risk window, where signals for abatacept, infliximab and rituximab were noted.

Conclusion The rate of ACS among patients with RA initiating bDMARDs remains elevated compared with the general population. As used in routine care, the short-term, intermediate-term and longer-term risks of ACS vary little across individual bDMARDs.

Key messages

What is already known about this subject?

⇒ Patients with rheumatoid arthritis (RA) are at increased risk of acute coronary syndrome (ACS) and other cardiovascular diseases, but how different biologic/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) compare to each other with regard to these risks remains unclear, and most studies have compared risks with one b/tsDMARD to another rather than all available b/tsDMARDs to each other.

What does this study add?

⇒ In this Nordic collaborative study, we demonstrate that patients with RA initiating b/tsDMARDs in routine care are at an 80% more elevated risk of ACS than the general population, but as used in routine care, the short-term, intermediate-term and longer-term risks of ACS vary little across individual bDMARDs.

How might this impact on clinical practice or future developments?

⇒ As used in routine clinical practice, the short-term, intermediate-term and longer-term incidences of ACS vary little across individual bDMARDs.

INTRODUCTION

Patients with rheumatoid arthritis (RA) are at increased risk of cardiovascular (CV) diseases (CVDs), presumably due to a higher prevalence of traditional CV risk factors, effects of the inflammatory disease and, potentially also, direct or indirect effects of its treatment.[1–9] Efficacious treatment of RA inflammation should reduce CV disease burden in RA,[10–13] but while the absolute risks of CV events in the general population and in cohorts of patients with RA have declined substantially during the past decades, studies from recent years suggest that a gap in CV risk remains between these two populations.[5 14–18]

Antirheumatic therapies (here: biologic (b)/targeted synthetic (ts) disease-modifying antirheumatic drugs (DMARDs)) potentially play a role for (closing of) the gap.[6] Besides suppressing RA-related inflammation, different b/tsDMARDs (as well as conventional synthetic DMARDs, oral corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs)) have by themselves been linked to detrimental as well as beneficial effects on CV disease risks.[10 12 13 19–22] For instance, tumour necrosis factors inhibitors (TNFis) may aggravate heart failure, tocilizumab and rituximab may

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alter lipid levels and Janus kinase inhibitors may also induce lipid alterations.[10 23–25] In the relative absence of head-to-head CV prevention trials of all DMARDs against each other in RA, observational studies have assessed various aspects of CV risks related to biologic DMARDs (bDMARDs), with somewhat varying results.[10 11] However, most of the studies on this topic have compared one drug or one class of drugs (eg, TNFi to csDMARDs) to another, rather than comparing all individual drugs,[6 20 26] while from a clinical decision-making point of view, results on individual drugs could also be of interest. Further, long-term studies on CV risks with b/tsDMARDs are sparse.[12 13]

For these reasons, we aimed to study the short-term (1 year), intermediate-term (2 years) and longer-term (5 years) incidences of acute coronary syndrome (ACS) in patients initiating b/tsDMARDs, taking relevant other factors into account. We further compared the ACS incidences in this RA population to the general population.

SUBJECTS AND METHODS

Design and setting

We performed an observational cohort study using prospectively collected individual-level data from the clinical rheumatology registers in Denmark (DANBIO), Finland (ROB-FIN), Norway (NOR-DMARD) and Sweden (SRQ-ARTIS).[27–31] In each country, linkages of the clinical data to other national registers were performed in order to identify data on past and incident ACS events, covariates (see definitions below), emigration and vital status throughout the study period from 1 January 2008 (1 January 2009 for Norway) to 31 December 2017.[30]

Study population and exposure

We defined ten drug-specific treatment cohorts as all initiators of: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, rituximab, tocilizumab, baricitinib and tofacitinib (the low number of patients and the short follow-up precluded meaningful analyses of the latter two drugs). One patient could contribute to several treatment cohorts (eg, a patient starting etanercept, later switching to tocilizumab, contributed to both cohorts). For all treatments, the number of previous b/tsDMARDs the patient had been exposed to was retrieved. Patients were included irrespective of history of ischaemic heart disease, including ACS.

Outcome

In each cohort, ACS during follow-up was defined as the first registered event of hospitalisation due to either unstable angina (International Classification of Diseases 10th Revision (ICD-10) I20.0) or acute myocardial infarction (MI) (transmural MI ICD-10 I21.0, I21.1, I21.2, I21.3; subendocardial MI ICD-10 I21.4; unspecific MI I21.9), as identified via linkage to the national patient registers.[30] In Sweden, the definition also included deaths stating ICD-10 I21 or I20.0 as main cause.

Covariates

Using the registers' linkage,[30] we identified baseline (ie, at treatment start) covariates for each treatment cohort: demographics (eg, sex), clinical (eg, C reactive protein (CRP)), comedication (eg, methotrexate), comorbidities (eg, history of a thromboembolic event) and related medications (eg, use of anticoagulants) and other information (eg, number of previous hospitalisations), see online supplemental table 1.

Follow-up and risk windows

For each treatment cohort, follow-up began at the start of the b/tsDMARD in question. Any treatment interruption (of the same drug) shorter than 3 months was disregarded. Since patients are recorded as being on a specific treatment rather than with, for example, their dates of dispensation, the treatment interruptions' rule did not affect the handling of rituximab data. We made no distinction between originator products and their biosimilars.

We applied five different definitions of the follow-up. First, (1) we used an 'on-drug' approach with follow-up stop being defined as the first of: first registered ACS, emigration, death, 90 days after any discontinuation of the treatment under study, 2 years after treatment start and end of the study period and (2) same as (1) but 5 years (instead of 2 years) after treatment start. Then, an 'ever since treatment start' approach was used in which any drug discontinuation disregarded was also used with a maximum of (3) 1-year, (4) 2-year and (5) 5-year follow-up (online supplemental figure 1). The 'on-drug' approach is conceptually similar to an 'as-treated' approach used in randomised controlled trials (RCT), while the 'ever since treatment start' is similar to an intention-to-treat approach.[32] This latter approach could result in one event being attributed to more than one medication.

General population comparator

We identified general population cohorts (available in Denmark and Sweden only) and (through the same type of register linkages) ACS events within these cohorts. We selected each RA patient's first b/tsDMARD-treatment record to define a cohort of unique RA patients. The general population comparator cohort was individually matched (1:10 in Denmark and 1:5 in Sweden) to these, on sex, age and area of residence. As for the patients with RA, general population controls were included irrespective of history of ischaemic heart disease, including ACS.

Statistical analyses

Online supplemental table 2 contains an overview of the analyses performed according to pooling of data across countries and follow-up definitions. We assessed descriptive statistics at baseline for each treatment cohort and in each country, in each country (pooling treatments) or for each treatment (pooling countries). Because of the low number of patients and follow-up, the baricitinib and tofacitinib cohorts were only included in this descriptive part. For the bDMARD cohorts, we computed the number of ACS events, follow-up-times at risk and crude incidence rates (IRs) of ACS in each treatment cohort, for the five follow-up definitions and per country and treatment. We compared the association between individual bDMARDs and incident ACS using Cox regression, with etanercept as reference, time since treatment start as time scale and a robust sandwich estimator to account for the correlated data structure. Further, as statistical heterogeneity among countries for each treatment was low (I^2 statistic<25%), analyses were performed on pooled data and stratified by country (ie, stratified Cox). We used four successively adjusted analyses models: model 1 provided crude HRs (ie, the relative rates as observed in the clinic); model 2 adjusted for age, sex and calendar period of bDMARD start (2008–2013 vs 2014–2017); model 3 additionally included the number of previous b/tsDMARDs, history of ACS, RA seropositivity and CRP level and model 4 additionally adjusted for smoking, number of hospitalisations, accumulated dose of prednisolone, concomitant use of methotrexate, history of hypertensive or cardiac disease (other than ACS), thromboembolic or cerebrovascular events, presence of

diabetes, presence of at least one among the five following diseases/comorbidities: kidney disease, affective disorder, chronic obstructive pulmonary disease (COPD), hospitalised infection and cancer and prescription of at least one of the five following drugs: anticoagulants, aspirin, ACE, beta-calcium and lipid-lowering drug. Norwegian data were missing information on several of these variables and were not included in model 4. Variables included for adjustment were measured at baseline and predetermined. Smoking and RA seropositivity included a 'missing' category. CRP was categorised in quartiles and a 'missing' category was added to these. Otherwise, no imputation was performed for other variables. In all tabulations, cells with less than five ACS events are displayed as 'N/A' and no HRs were assessed. Data analyses were performed in SAS, V.9.4.

Separate analyses in subgroups of patients

We performed the same Cox analyses separately by age (18–64 vs 65 years or older), number of previous b/tsDMARDs (none, one, two or more) and presence (yes vs no) of history of any CVD. For this latter analysis, a more extensive definition was applied to rule out previous CV risk and included history of hypertensive or cardiac disease (ACS and other), thromboembolic or cerebral event or prescription of anticoagulants, aspirin, ACE, beta-calcium or lipid-lowering drug. Additionally, the 5-year 'on-drug' analyses by treatment cohort were performed restricted to patients starting their first ever bDMARD.

Comparison with the general population

In the Cox analyses, the general population individuals and their index RA patients were followed up from treatment start of the index RA patient (irrespective of which b/tsDMARD was started) and onwards using an ever since treatment start approach with no imposed limit (other than the study period) in the follow-up duration. The Cox regression was run separately for the two countries with attained age as time scale, stratified on the matching variables and adjusted for history of previous ACS. In addition, the same analysis was performed for each bDMARD treatment cohort separately.

Patients' involvement

This study was performed within the context of a Nordic rheumatology registers collaboration, which employed a patient representatives panel.

RESULTS

Baseline characteristics

Overall, 24 083 patients were included (75% women, mean age 56 years) initiating 40 850 treatment courses. Of these, etanercept was the most common (10 866, 27% of all treatments courses), followed by adalimumab (14%), infliximab (13%), rituximab (12%), tocilizumab (10%), certolizumab pegol (9%), abatacept (9%), golimumab (6%) and baricitinib and tofacitinib (<1%). Overall, 47% of all treatment episodes were from Sweden (19 090 treatment episodes), 34% from Denmark and Finland and Norway contributed 14% and 6%, respectively. Overall, 60% of the treatment starts represented a first ever b/tsDMARD start and 20% a second.

Descriptive statistics for individual b/tsDMARD treatments (all countries pooled) are displayed in table 1. Patients starting rituximab tended to be older (median 62 years) than patients receiving other b/tsDMARDs (median ranging from 55 to 59 years). Compared with patients starting a TNFi, patients starting a non-TNFi bDMARD generally presented somewhat higher values for clinical variables (CRP, erythrocyte sedimentation rate, patient's global health assessment, pain, health assessment questionnaire and disease activity score with CRP (DAS28CRP)), had been exposed to more previous b/tsDMARDs and more often had comorbidities (COPD, diabetes, history of CV event, history of kidney disease and history of infection). Overall, 30% of the patients on rituximab had a history of hypertensive or cardiac disease, while this proportion was less than 20% for patients on TNFi and between 20% and 25% for the other non-TNFi bDMARDs and tsDMARDs. Patients starting a tsDMARD or non-TNFi bDMARD had a larger accumulated dose of prednisolone than patients starting a TNFi. Intercountry differences were small, overall and by treatment (online supplemental tables 3 and 4).

Occurrence of ACS

During the maximum follow-up (5 years, ever since treatment start) amounting to 141 257 person-years (pyrs), we observed a total of 780 incident ACS events, corresponding to a crude IR of 5.5 per 1000 pyrs. The 5-year 'on-drug' crude IR was similar. The corresponding numbers for the shortest follow-up definition (1 year, ever since treatment start) were 215 incident ACS during 38 102 pyrs and a crude IR of 5.6 per 1000 pyrs (table 2). For almost all follow-up definitions, rituximab was associated with the highest crude ACS incidences, table 2 and online supplemental table 5.

Comparison of risks (HR) in individual bDMARDs

Online supplemental table 6 displays crude and successively adjusted HRs, by treatment and by follow-up definition. Across all comparisons (ie, all follow-up definitions), there was a consistent pattern of statistically significantly elevated HRs for abatacept and rituximab in crude models (HRs ranging from 1.6 to 2.3) the magnitude of which decreased and lost its statistical significance with successive adjustments, so that in the fully adjusted model, HRs for abatacept and rituximab ranged between 1.1 and 1.3. The HRs for infliximab increased slightly with increasing length of follow-up, reaching 1.49 (1.08–2.05) for the 5-year follow-up 'on drug'. For the other bDMARDs, HRs were close to 1 (online supplemental table 6 and figure 1).

Separate analyses in subgroups of patients defined by the number of previous b/tsDMARDs showed that, among patients starting their first or second bDMARD, none of the drugs were more (nor less) associated with ACS, with the exception of abatacept ('on-drug' analysis only) (online supplemental table 7, upper panel and figure 2). By contrast, among patients starting their third or more bDMARD and followed up for 5 years, all HRs were higher with the HRs for abatacept, infliximab and rituximab borderline or statistically significantly increased (figure 2). The analyses performed by age group (18–64 and 65+ years) provided results similar to the main analysis (online supplemental table 7, median panel and figure 2). Excluding all patients with a history of any CVD resulted in a pattern of HRs largely similar to those of the main analysis (online supplemental table 7, lower panel and figure 2). Finally, in patients with a history of any CVD, all HRs were close to one with the exception of infliximab for which the HR was 1.49 (1.02–2.18) for the 5-year follow-up, 'on-drug' approach (online supplemental table 7, lower panel and figure 2).

Table 1 Baseline characteristics for each treatment cohort (all countries pooled together)

	Treatment cohorts									
	TNFi					Non-TNFi bDMARD			tsDMARDs	
Variables	Etanercept	Adalimumab	Certolizumab pegol	Golimumab	Infliximab	Abatacept	Rituximab	Tocilizumab	Baricitinib	Tofacitinib
N (treatment) (%)	10 866 (%)	5751	3820	2415	5349	3610	4781	3989	164	105
Distribution of treatments										
Denmark	3230	1982	1495	443	2208	1290	1216	1793	23	9
Finland	1329	983	433	521	309	580	1093	482	28	31
Norway	543	202	521	167	252	110	271	202	0	14
Sweden	5764	2584	1371	1284	2580	1630	2201	1512	113	51
N unique patients*	10 229	5430	3733	2357	5088	3466	4591	3724	164	104
Women, n (%)	8339 (77%)	4384 (76%)	2868 (75%)	1824 (76%)	3944 (74%)	2876 (80%)	3583 (75%)	3110 (78%)	128 (78%)	82 (78%)
Year of birth	1956 (1947–1967)	1955 (1947–1966)	1956 (1948–1967)	1958 (1948–1969)	1955 (1946–1966)	1955 (1946–1965)	1950 (1943–1960)	1956 (1947–1965)	1959 (1950–1969)	1962 (1953–1970)
Age, years	57(46–66)	56 (45–64)	57 (46–65)	55 (44–65)	58 (47–66)	59 (49–68)	62 (53–70)	58(48–67)	58(48–67)	55(47–64)
Disease duration										
Less than 1 year	667 (6.3)	311 (5.6)	306 (8.5)	150 (6.5)	382 (7.4)	156 (4.5)	157 (3.4)	204 (5.3)	1 (0.6)	2 (2.1)
1–5 years	3675 (34.9)	1789 (32.3)	1255 (35)	771 (33.6)	1918 (37.3)	1005 (28.8)	1089 (23.8)	1151 (30)	35 (22)	26 (27.1)
More than 5 years	6177 (58.7)	3443 (62.1)	2022 (56.4)	1375 (59.9)	2841 (55.3)	2325 (66.7)	3327 (72.8)	2479 (64.7)	123 (77.4)	68 (70.8)
Number of previous b/tsDMARDs, n										
0	6303 (58.1)	3087 (53.7)	2257 (59.3)	1284 (53.2)	3925 (73.5)	900 (25)	1856 (38.9)	793 (19.9)	17 (10.4)	16 (15.4)
1	3181 (29.3)	1905 (33.1)	853 (22.4)	641 (26.6)	859 (16.1)	904 (25.1)	1143 (23.9)	1060 (26.6)	30 (18.3)	18 (17.3)
2+	1371 (12.6)	756 (13.2)	699 (18.4)	488 (20.2)	557 (10.4)	1803 (50)	1774 (37.2)	2132 (53.5)	117 (71.3)	70 (67.3)
Year of treatment start	2013 (2010–2016)	2011 (2009–2013)	2013 (2012–2015)	2013 (2011–2015)	2013 (2010–2016)	2014 (2013–2016)	2013 (2011–2015)	2014 (2012–2016)	2017 (2017–2017)	2017 (2017–2017)
Seropositivity†										
Negative, n (%)	1750 (16%)	908 (16%)	587 (15%)	394 (16%)	821 (15%)	525 (15%)	357 (7%)	599 (15%)	31 (19%)	16 (15%)
Positive, n (%)	5281 (49%)	2694 (47%)	1746 (46%)	1113 (46%)	2531 (47%)	1789 (50%)	2477 (52%)	1852 (46%)	93 (57%)	51 (49%)
Unknown, n (%)	3835 (35%)	2149 (37%)	1487 (39%)	908 (38%)	1997 (37%)	1296 (36%)	1947 (41%)	1538 (39%)	40 (24%)	38 (36%)
Clinical variables										
CRP (mg/L)	7.0 (3.0–19.0)	8.0 (3.0–20.0)	7.0 (3.0–17.0)	6.0 (3.0–18.0)	8.0 (3.0–20.0)	8.0 (3.0–21.0)	10.0 (4.65–25.0)	11.0 (4.0–29.0)	6.0 (3.0–13.0)	5.9 (2.0–15.0)
ESR (mm/h)—not available in Denmark	18.0 (9.0–33.0)	18.0 (8.0–32.0)	17.0 (8.0–30.0)	16.0 (7.0–31.0)	19.0 (10.0–36.0)	21.0 (10.0–40.0)	24.0 (12.0–42.0)	24.0 (12.0–43.0)	19.0 (7.0–35.0)	15.0 (7.0–34.0)
28 SJC	4.0 (2.0–7.0)	4.0 (2.0–7.0)	4.0 (1.0–7.0)	3.0 (1.0–7.0)	4.0 (1.0–8.0)	4.0 (2.0–7.0)	5.0 (2.0–8.0)	4.0 (2.0–8.0)	4.0 (2.0–8.0)	4.0 (1.5–7.0)
28 TJC	5.0 (2.0–10.0)	5.0 (2.0–10.0)	5.0 (2.0–10.0)	5.0 (2.0–9.0)	6.0 (2.0–10.0)	6.0 (3.0–11.0)	6.0 (2.0–10.0)	6.0 (3.0–12.0)	5.0 (2.0–10.0)	6.0 (3.0–10.0)
PGHA (VAS: 0–100)	59 (37–77)	59 (37–75)	61 (40–78)	53 (30–73)	61 (39–79)	65 (45–80)	61 (40–78)	68 (47–83)	60 (34–75)	68 (44–84)
Pain (VAS: 0–100)	58 (35–75)	57 (34–74)	59 (35–75)	54 (30–73)	57 (35–75)	63 (42–77)	60 (38–76)	64 (43–79)	60 (31–73)	60 (38–79)
HAQ	1.0 (0.6–1.6)	1.0 (0.6–1.6)	1.3 (0.8–2.0)	1.0 (0.5–1.6)	1.1 (0.6–1.8)	1.3 (0.9–1.9)	1.3 (0.9–1.9)	1.4 (0.9–2.0)	1.1 (0.6–1.6)	1.4 (0.6–2.3)
DAS28CRP	4.41 (3.57–5.26)	4.49 (3.60–5.30)	4.40 (3.58–5.20)	4.23 (3.31–5.10)	4.50 (3.70–5.34)	4.65 (3.81–5.40)	4.70 (3.80–5.50)	4.80 (3.90–5.60)	4.39 (3.60–5.16)	4.56 (3.84–5.27)
Comedication										
Concomitant csDMARD	6217 (57%)	3577 (62%)	2475 (65%)	1465 (61%)	3559 (67%)	1950 (54%)	2572 (54%)	1748 (44%)	61 (37%)	46 (44%)

Continued

Table 1 Continued

Variables	Treatment cohorts									
	TNFi					Non-TNFi bDMARD			tsDMARDs	
	Etanercept	Adalimumab	Certolizumab pegol	Golimumab	Infliximab	Abatacept	Rituximab	Tocilizumab	Baricitinib	Tofacitinib
Concomitant methotrexate	5180 (48%)	3025 (53%)	2001 (52%)	1237 (51%)	3117 (58%)	1600 (44%)	1959 (41%)	1384 (35%)	41 (25%)	35 (33%)
Accumulated prednisolon dose (mg)	2000 (500–4750)	1750 (150–4500)	1500 (0–4500)	2000 (500–4700)	1500 (0–4000)	2500 (500–6500)	3250 (1000–7000)	2500 (500–6125)	3750 (1000–7500)	4000 (1000–7500)
Comorbidities										
History of:										
ACS event	157 (1%)	84 (1%)	50 (1%)	25 (1%)	91 (2%)	85 (2%)	118 (2%)	73 (2%)	1 (1%)	0 (0%)
Hypertensive or cardiac disease	2140 (20%)	1013 (18%)	683 (18%)	414 (17%)	1006 (19%)	915 (25%)	1428 (30%)	902 (23%)	37 (23%)	21 (20%)
Cerebral event	216 (2%)	81 (1%)	70 (2%)	41 (2%)	96 (2%)	99 (3%)	145 (3%)	94 (2%)	3 (2%)	0 (0%)
Thrombembolic event	116 (1%)	60 (1%)	54 (1%)	19 (1%)	45 (1%)	71 (2%)	107 (2%)	55 (1%)	3 (2%)	2 (2%)
Diabetes	851 (8%)	401 (7%)	232 (6%)	138 (6%)	408 (8%)	333 (9%)	483 (10%)	319 (8%)	14 (9%)	10 (10%)
Kidney disease	110 (1%)	42 (1%)	29 (1%)	15 (1%)	32 (1%)	60 (2%)	82 (2%)	62 (2%)	1 (1%)	0 (0%)
Hospitalised infection	1392 (13%)	688 (12%)	498 (13%)	284 (12%)	608 (11%)	704 (20%)	1092 (23%)	691 (17%)	31 (19%)	20 (19%)
COPD	958 (9%)	452 (8%)	337 (9%)	149 (6%)	445 (8%)	466 (13%)	636 (13%)	457 (11%)	12 (7%)	11 (10%)
Cancer	221 (2%)	83 (1%)	69 (2%)	46 (2%)	85 (2%)	100 (3%)	487 (10%)	104 (3%)	1 (1%)	2 (2%)
Affective disorder	1420 (14%)	676 (12%)	449 (14%)	286 (13%)	701 (14%)	539 (15%)	645 (14%)	568 (15%)	31 (19%)	19 (21%)
Number of hospitalisations, n	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–3)	1 (0–2)	1 (0–3)	2 (0–5)	1 (0–3)	1 (0–3)	2 (0–3)
Drug prescription										
Beta-calcium	2711 (26%)	1342 (24%)	818 (25%)	522 (23%)	1293 (25%)	1101 (31%)	1633 (36%)	1105 (29%)	45 (27%)	27 (30%)
Anticoagulant	447 (5%)	182 (4%)	118 (4%)	66 (4%)	190 (4%)	199 (7%)	314 (9%)	187 (6%)	11 (8%)	4 (7%)
ACE inhibitors	2178 (21%)	1070 (19%)	618 (19%)	463 (21%)	1047 (21%)	894 (26%)	1248 (28%)	871 (23%)	40 (24%)	21 (23%)
Lipid lowering	1413 (14%)	736 (13%)	450 (14%)	275 (12%)	764 (15%)	596 (17%)	880 (20%)	566 (15%)	28 (17%)	10 (11%)
Aspirin	972 (11%)	467 (10%)	293 (10%)	152 (9%)	534 (11%)	384 (13%)	555 (16%)	379 (11%)	10 (7%)	5 (8%)
At least one of these five drugs	4160 (38%)	2073 (36%)	1250 (33%)	835 (35%)	2045 (38%)	1638 (45%)	2368 (50%)	1677 (42%)	73 (45%)	35 (33%)
Smoking										
Current	1310 (12.1)	679 (11.8)	552 (14.5)	258 (10.7)	778 (14.5)	463 (12.8)	548 (11.5)	612 (15.3)	18 (11)	12 (11.4)
Former	3523 (32.4)	1697 (29.5)	1107 (29)	719 (29.8)	1720 (32.2)	1140 (31.6)	1457 (30.5)	1228 (30.8)	64 (39)	28 (26.7)
Never	4079 (37.5)	2050 (35.6)	1483 (38.8)	905 (37.5)	2099 (39.2)	1360 (37.7)	1612 (33.7)	1579 (39.6)	57 (34.8)	34 (32.4)
Missing	1954 (18)	1325 (23)	678 (17.7)	533 (22.1)	752 (14.1)	647 (17.9)	1164 (24.3)	570 (14.3)	25 (15.2)	31 (29.5)

Medians (quartiles) for continuous variables and number (percentages) for binary variables are displayed. If not otherwise specified, the statistics pertain to treatment episodes.
*Patients were allowed starting a treatment with the same molecule several times.
†Seropositivity assessed with both ACPA and RF: Positive if at least one of ACPA/RF is positive; negative if neither is positive and at least one is negative and unknown otherwise.
ACPA/RF, anti-citrullinated protein antibody/rheumatoid factor; ACS, acute coronary syndrome; b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; csDMARD, conventional synthetic DMARD; DAS28CRP, disease activity score based on 28 joints counts and CRP; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; PGHA, patient's global health assessment; 28 SJC, 28 swollen joint count; 28 TJC, 28 tender joint count; TNFi, tumour necrosis factors inhibitor; VAS, Visual Analogue Scale.

Table 2 Number of events per person-years (pyrs), crude incidence rates (IRs) (95% CIs) per 1000 pyrs in each treatment cohort, for 1-year, 2-year and 5-year follow-up lengths, 'on-drug' and 'ever since treatment start' follow-up definitions

	Two-year follow-up, 'on drug'		Five-year follow-up, 'on drug'		One-year follow-up, 'ever since treatment start'		Two-year follow-up, 'ever since treatment start'		Five-year follow-up, 'ever since treatment start'	
bDMARD	Event/pyrs	Crude IR/1000 pyrs (95% CI)	Event/pyrs	Crude IR/1000 pyrs (95% CI)	Event/pyrs	Crude IR/1000 pyrs (95% CI)	Event/pyrs	Crude IR/1000 pyrs (95% CI)	Event/pyrs	Crude IR/1000 pyrs (95% CI)
TNFi										
Etanercept	70/13 411	5.2 (4.1 to 6.6)	98/21 326	4.6 (3.8 to 5.6)	49/9885	5.0 (3.8 to 6.6)	91/17 922	5.1 (4.1 to 6.2)	175/35 917	4.9 (4.2 to 5.7)
Adalimumab	31/7669	4.0 (2.8 to 5.8)	54/12 704	4.3 (3.3 to 5.6)	27/5613	4.8 (3.3 to 7.0)	50/10 887	4.6 (3.5 to 6.1)	115/24 093	4.8 (4.0 to 5.7)
Certolizumab pegol	20/4633	4.3 (2.8 to 6.7)	27/6871	3.9 (2.7 to 5.7)	15/3718	4.0 (2.4 to 6.7)	29/7158	4.1 (2.8 to 5.8)	54/14 158	3.8 (2.9 to 5.0)
Golimumab	7/3262	2.2 (1.0 to 4.5)	15/5088	3.0 (1.8 to 4.9)	7/2349	3.0 (1.4 to 6.3)	14/4534	3.1 (1.8 to 5.2)	40/9006	4.4 (3.3 to 6.1)
Infliximab	40/6602	6.1 (4.4 to 8.3)	67/9462	7.1 (5.6 to 9.0)	22/4994	4.4 (2.9 to 6.7)	48/9225	5.2 (3.9 to 6.9)	106/17 803	6.0 (4.9 to 7.2)
Non-TNFi bDMARD										
Abatacept	36/4352	8.3 (6.0 to 11.5)	49/6099	8.0 (6.1 to 10.6)	26/3356	7.8 (5.3 to 11.4)	50/6164	8.1 (6.2 to 10.7)	70/10 795	6.5 (5.1 to 8.2)
Rituximab	64/6663	9.6 (7.5 to 12.3)	98/10 993	8.9 (7.3 to 10.9)	51/4466	11.4 (8.7 to 15.0)	82/8335	9.8 (7.9 to 12.2)	158/16 619	9.5 (8.1 to 11.1)
Tocilizumab	26/5030	5.2 (3.5 to 7.6)	36/7771	4.6 (3.3 to 6.4)	18/3721	4.8 (3.1 to 7.7)	34/6869	5.0 (3.5 to 6.9)	62/12 866	4.8 (3.8 to 6.2)

'On drug': follow-up ended at acute coronary syndrome (ACS) event, censoring or treatment discontinuation. 'Ever since treatment start': follow-up ended at ACS event or censoring (ie, treatment discontinuation was disregarded).
b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug; TNFi, tumour necrosis factors inhibitor.

Comparison with the general population

Pyrs, mean follow-up times and crude incidences of ACS for the general population comparator cohorts were 304 612 pyrs, 4.8 years and 2.4/1000 pyrs for Denmark and 239 873 pyrs, 4.5 years and 3.6/1000 pyrs for Sweden, which, compared with the RA populations (37 175 pyrs, 5.1 years and 4.5/1000 pyrs in Denmark and 51 193 pyrs, 4.4 years and 6.6/1000 pyrs in Sweden) resulted in HRs (95% CI) of 1.8 (1.5–2.1) for Denmark and 1.8 (1.6–2.0) for Sweden, taking the matching factors (age, sex and calendar time) and history of ACS into account. Treatment-specific analyses showed that every bDMARDs were associated with a higher IR of ACS compared with the general

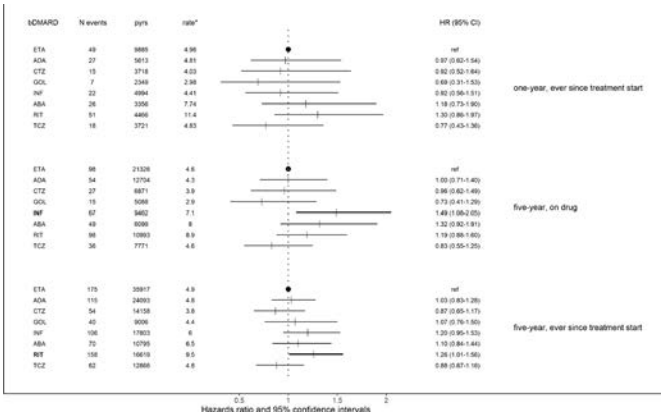

Figure 1 Number of events, person-years (pyrs), crude incidence rates per 1000 pyrs for each bDMARD treatment cohort, HRs obtained from Cox analyses (95% CIs), using etanercept as reference, for the shortest (, ever since treatment start, 1-year) and the longest (ever since treatment start, 5 years) risk windows. *Rate: rate per 1000 pyrs. ABA, abatacept; ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; CTZ, certolizumab pegol; ETA, etanercept; GOL, golimumab; INF, infliximab; RIT, rituximab; TCZ, tocilizumab.

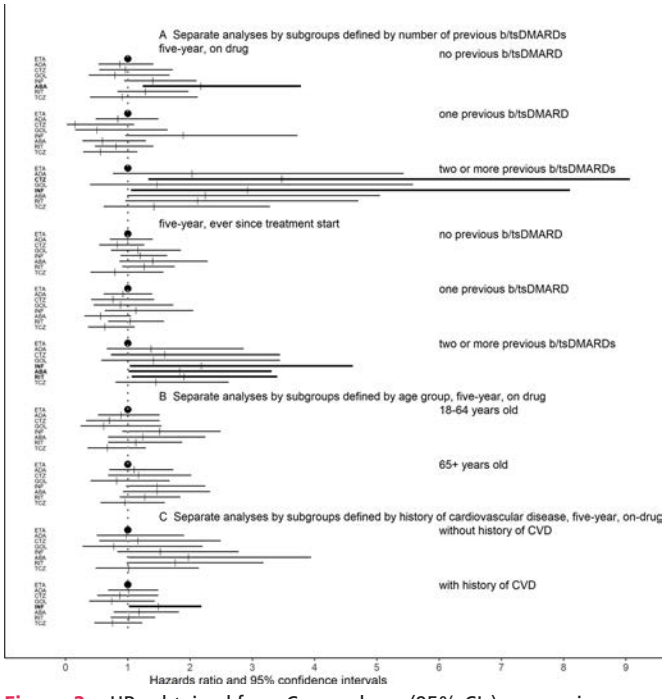

Figure 2 HRs obtained from Cox analyses (95% CIs), comparing the rates for each bDMARD to that for etanercept, for a 5-year follow-up length, and fully adjusted model (model 4). Analyses were performed separately on subgroups defined by (A) number of previous b/tsDMARDs (no vs one vs two or more), 'on-drug' and 'ever since treatment start' approaches, (B) age (18–64 vs 65+ years), 'on drug' and (C) history of cardiovascular disease (CVD) (without vs with), 'on drug'. ABA, abatacept; ADA, adalimumab; b/tsDMARDs, biologic/targeted synthetic disease-modifying antirheumatic drugs; CTZ, certolizumab pegol; ETA, etanercept; GOL, golimumab; INF, infliximab; RIT, rituximab; TCZ, tocilizumab.

population (online supplemental table 8). The HR (95% CI) for etanercept was around 1.5 in both countries.

DISCUSSION

In this study of almost 41 000 treatment episodes of bDMARDs and covering population-based data from four Nordic countries, we observed that the IR of ACS in patients with RA initiating treatment with a bDMARD was around 80% higher than in the general population. Comparing the bDMARDs to each other, we noted little differences in ACS rates in the short and intermediate terms. In the longer term, initiation of abatacept, infliximab and rituximab was associated with a moderately increased rate of ACS, a finding which remained when patients with previous CVD were excluded, but was largely confined to patients starting their third or later b/tsDMARD.

Numerous studies have addressed aspects of CVD in patients with RA in relation to treatment, many of them reporting on beneficial effects of DMARDs (including methotrexate, TNFis and other bDMARDs) on CV risk factors such as glucose, cholesterol or lipid metabolism, blood pressure, endothelial function and arterial stiffness.[12 13 21 22 33–36] Most studies focusing on the association between treatment and CV risk have compared groups of drugs rather than individual ones, at least with regard to TNFis. Compared with non-bDMARDs, TNFis have a positive effect on the risk of CV events,[10 11 20 37–39] in particular among responders;[39–41] tocilizumab has been reported to exert marginally superior effects on CV outcomes compared with TNFis,[10 12 13] but results are conflicting.[25 42–44] No detrimental effect on CV outcomes of abatacept or rituximab have been reported.[12 13 42] One study reported greater benefit for TNFi non-responders who, as next bDMARD, received tocilizumab or abatacept instead of rituximab.[45]

The observed increased risk for abatacept, infliximab and rituximab in our study might be explained by residual confounding or confounding by indication. Patients on abatacept and rituximab had more comorbidities and longer disease duration with potentially longer exposure to inflammation, which is associated with CV risk.[46] As expected, adjusting for relevant factors generally led to a considerable attenuation of the strength of the association, but we cannot formally disentangle whether our results indicate an interaction (ie, that the 'true' risk of certain bDMARDs varies across subsets of patients with RA as defined by their treatment history) or reflect residual channelling bias. The potential protective effect of tocilizumab against ACS, as reported in Atzeni *et al*,[13] was not clearly supported by our results and remains to be clarified. Lastly, compared with the study by Xie *et al*,[42] which also compared individual bDMARDs (although with some differences in the source populations), the HRs in our study were generally closer to 1 and with narrower 95% CI.

Our study has limitations. Although we had access to ample data on comorbid conditions, demographics and clinical characteristics, we lacked information on socioeconomic data such as education level, sick leave and disability pension. We did not have information on concomitant NSAIDs or Cyclooxygenase-2 (COX-2) inhibitors. We also had too little data to allow any meaningful comparison of ACS risk in patients treated with tsDMARDs, for which the CV safety profile is currently questioned.[7 13 24 25 47] The comparison of patients with RA with the general population included patients with RA starting a b/tsDMARD treatment, hence representing the subset of the entire pool of RA ill enough to need a b/tsDMARD yet fit enough to be presumed to tolerate such treatment. The ACS definition also varied somewhat between countries which could impact the IRs but not the HRs as Cox analyses were stratified on the country variable. We also used ACS, which is a clinically well-defined entity, as outcome instead of the more heterogeneous composite 'major cardiovascular event' (MACE), in order to further reduce the potential for country-specific variations in the outcome construct, but limited the comparability of our results to, for example, trials using MACE as its single CV outcome.

Our study has several strengths, including its setting (the built-in possibility to compare and pool across five large RA source populations), its large number of subjects and events and the possibility to compare risks across different strata of patients and follow-up times. The use of register linkages and previously developed algorithms to define ACS and other variables ensured an independent (from exposure) assessment of ACS events, low risk of misclassification of exposure, outcomes and covariates and allowed adjustments for many potential confounders. Data on general population comparator subjects enabled contextualising of our findings. We employed multiple definitions of risk windows to enable assessment of both short-term, intermediate-term and longer-term risks. Finally, with the exception of tsDMARDs, our study allowed evaluation of risks by all clinically available bDMARD options rather than by one (drug or class) versus one other, the former being a reasonable point of departure from a clinical decision-making point of view.

To conclude, as used in routine care, the risks of ACS in patients with RA starting a bDMARD vary little across individual drugs for short and intermediate terms. This most likely also applies to the longer term despite signals of higher ACS incidence that are most probably linked to the treatment context including patient-related factors rather than to the drug per se. Thus, our results suggest that in RA treated with bDMARDs, the bDMARD used does not seem to matter for the risk of ACS.

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Contributors Substantial contribution to conception and design, reading and approval of the final version and revising the draft critically:BD, LL, SAP, BG, MLH, KLG, RP, HR, CT, BG, BM and JA . Analysis: BD. Interpretation of data: BD, LL, SAP, BG, MLH, KLG, HR, CT, BG, BM and JA. Drafting the article: BD, JA, LL, SAP and BG. Guarantor: JA.

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Competing interests LL: chairs the steering committee of the Swedish Rheumatology Quality Register, SRQ. Karolinska University Hospital and its principal investigator SRQ has had agreements for register data analyses with AbbVie,

Amgen, BMS, Eli Lilly, Galapagos, Janssen, Novartis, Pfizer, Sanofi, Sobi and UCB. BG: research grants: Pfizer, BMS, Sandoz and AbbVie. MLH: grants: AbbVie, Biogen, BMS, Celltrion, Eli Lilly Denmark A/S, Janssen Biologics B.V, Lundbeckfonden, MSD, Pfizer, Roche, Samsung Bioepis and Sandoz; chairs the steering committee of the Danish Rheumatology Quality Registry (DANBIO), which receives public funding from the hospital owners and funding from pharmaceutical companies, and cochairs Eurospa, which generates real-world evidence of treatment of psoriatic arthritis and axial spondyloarthritis based on secondary data and is partly funded by Novartis. KLG: grants: BMS. RP: lecturer: Actelion, Boehringer Ingelheim, Pfizer, Sanofi and Janssen; grants: Mylen and data safety monitoring: Boehringer Ingelheim, Lilly, Janssen and AbbVie. HR: Congress fees and speaker fees from AbbVie and consulting fees: Celgene and Pfizer. CT: speaker fees: AbbVie, Bristol-Myers Squibb, Nordic Drugs, Pfizer and Roche. BG: consultant and lecturer fees: Novartis. BM: research grant (paid to employer) and consultancy fees: Novartis. JA: grants: AbbVie, Astra-Zeneca, BMS, Eli Lilly, Galapagos, MSD, Pfizer, Roche, Samsung Bioepis, Sanofi and UCB. AbbVie, Astra-Zeneca, BMS, Eli Lilly, MSD, Pfizer, Roche, Samsung Bioepis, Sanofi, and UCB have entered into agreements with Karolinska Institutet with JA as principal investigator, mainly in the context of safety monitoring of biologics via the ARTIS national safety monitoring system.

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 applicable.

Ethics approval Denmark: ethical approval not required for registry studies (komitelovens §14, stk. 2, www.nvk.dk), Capital region data-protection office RH-2015–209 and Isuite 04145; Finland: ethical approval—FI: 73/13/03/00/2014; Norwegian: Regional Committees for Medical and Health Research Ethics South East (Ref. 2019/329/REK sør-øst) and Sweden: the Swedish Ethical Review Authority, 2015/1844-31/2.

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EPIDEMIOLOGICAL SCIENCE

Tofacitinib and risk of cardiovascular outcomes: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) study

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ABSTRACT

Objectives Recent results from 'ORAL Surveillance' trial have raised concerns regarding the cardiovascular safety of tofacitinib in patients with rheumatoid arthritis (RA). We further examined this safety concern in the real-world setting.

Methods We created two cohorts of patients with RA initiating treatment with tofacitinib or tumour necrosis factor inhibitors (TNFI) using deidentified data from Optum Clinformatics (2012–2020), IBM MarketScan (2012–2018) and Medicare (parts A, B and D, 2012–2017) claims databases: (1) A 'real-world evidence (RWE) cohort' consisting of routine care patients and (2) A 'randomised controlled trial (RCT)-duplicate cohort' mimicking inclusion and exclusion criteria of the ORAL surveillance trial to calibrate results against the trial findings. Cox proportional hazards models with propensity score fine stratification weighting were used to estimate HR and 95% CIs for composite outcome of myocardial infarction and stroke and accounting for 76 potential confounders. Database-specific effect estimates were pooled using fixed effects models with inverse-variance weighting.

Results In the RWE cohort, 102 263 patients were identified of whom 12 852 (12.6%) initiated tofacitinib. The pooled weighted HR (95% CI) comparing tofacitinib with TNFI was 1.01 (0.83 to 1.23) in RWE cohort and 1.24 (0.90 to 1.69) in RCT-duplicate cohort which aligned closely with ORAL-surveillance results (HR: 1.33, 95% CI 0.91 to 1.94).

Conclusions We did not find evidence for an increased risk of cardiovascular outcomes with tofacitinib in patients with RA treated in the real-world setting; however, tofacitinib was associated with an increased risk of cardiovascular outcomes, although statistically non-significant, in patients with RA with cardiovascular risk factors.

Trial registration number NCT04772248.

Key message

What is already known about this subject?

⇒ Recently released topline findings from 'ORAL Surveillance' postmarketing trial have raised concerns that tofacitinib, in comparison with tumour necrosis factor inhibitors, may increase the risk of cardiovascular disease in patients with rheumatoid arthritis.

What does this study add?

⇒ In this multidatabase, population-based study including 102 263 rheumatoid arthritis patients, tofacitinib was not associated with an increased risk of cardiovascular outcomes when compared with tumour necrosis factor inhibitors.

⇒ A numerically increased risk of cardiovascular outcomes was observed in older patients with cardiovascular risk factors or history of cardiovascular disease.

How might this impact on clinical practice or future developments?

⇒ In this study in real-world setting, tofacitinib, in comparison with tumour necrosis factor inhibitors, was not associated with increased risk of cardiovascular outcomes, although an increased risk of cardiovascular outcomes with tofacitinib cannot be ruled out in patients with cardiovascular risk factors or history of cardiovascular disease.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects approximately 0.2% of adults worldwide.[1] RA is characterised by systemic inflammation that leads to joint damage and extra-articular manifestations including cardiovascular (CV) disease (CVD) that adversely impact morbidity and mortality. Janus kinase (JAK) inhibitors (consisting of tofacitinib, baricitinib, upadacitinib) are a class of targeted synthetic disease-modifying antirheumatic drugs (DMARDs) that are increasingly used for management of patients diagnosed with moderate to severely active RA.[2 3] Tofacitinib, first approved in USA in 2012, is the most commonly prescribed JAK inhibitor.[2 4]

Tofacitinib has been associated with improved disease control in patients with RA with similar efficacy when compared with other biological DMARDs (bDMARDs) such as adalimumab.[5–7] However, recent reports have from the 'ORAL Surveillance' postmarketing safety trial have indicated a potential for increased risk of major adverse CV events (MACE) with tofacitinib, in comparison with tumour necrosis factor inhibitors (TNFI), among patients with RA at least 50 years of age and with at least one risk factor for CVD (HR 1.33, 95% CI 0.91 to 1.94).[8–10] Thus, the aim of this study was to conduct a large population-based observational study to further examine the risk of

CV outcomes with tofacitinib in patients with RA treated in routine clinical care settings.

METHODS

Data sources and study design

We conducted a new user, active comparator cohort study (online supplemental figure 1) using claims data from the Optum Clinformatics (November 2012–June 2020), IBM MarketScan (November 2012–December 2018), and Medicare (parts A, B and D, November 2012–December 2017) databases.[11] The Optum and MarketScan claims databases capture de-identified record of over 200 million and 78 million commercially insured patients respectively in the USA. Medicare is a federal health insurance programme and provides healthcare coverage for residents of the USA aged at least 65 years and patient aged less than 65 with a disability status as ascertained by US Social Security Administration. All three data sources provide longitudinal information including patient demographics, inpatient and outpatient medical diagnoses and procedures, and prescription dispensing records. The protocol for this study was registered on ClinicalTrials.gov (NCT04772248) and reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[12 13] Requirement for patient informed consent was waived because all personal identifiers were removed from each of the datasets to ensure patient confidentiality. Signed data licence agreements were obtained for all data sources.

Study population

The base population consisted of patients initiating treatment on tofacitinib or a TNFI (infliximab, adalimumab, certolizumab pegol, etanercept and golimumab). Cohort entry date corresponded to first TNFI or tofacitinib dispensation ('index drug') with a minimum of 365 days of continuous enrollment in health plan prior to and including the cohort entry date. Patients required at least two diagnosis codes for RA in any setting during the 365 days baseline period (between 7 and 365 days apart).[14] A previous validation study demonstrated a positive predictive value of 86% for this claims-based algorithm which combines two diagnosis codes for RA with one DMARD dispensing record.[14] To ensure the inclusion of new users, we excluded TNFI users with a prescription of index TNFI and tofacitinib users with prescription of tofacitinib in the 365 days prior to cohort entry date. We also excluded patients with a prescription of tofacitinib and TNFI on cohort entry date, patients missing data on age or gender, and those with admission to nursing facility or hospice on or prior to cohort entry date. TNFI users with history of use of any JAK inhibitor or with prescriptions for multiple agents from the TNFI class on cohort entry date were also excluded. Finally, tofacitinib users with prescriptions of other approved JAK inhibitors (ie, baricitinib or upadacitinib) on or at any point prior to cohort entry date were excluded.

From this source population of patients with RA initiating treatment with tofacitinib or TNFI, we created two study cohorts. The first cohort, 'real-world evidence (RWE)', included all patients with RA from routine care. The RWE cohort included patients at least 18 years of age in MarketScan and Optum (≥65 in Medicare) at cohort entry date. The second cohort, 'randomised controlled trial (RCT)-duplicate cohort', mimicked the inclusion and exclusion criteria of the ORAL surveillance trial.[9] This study population was used to calibrate our findings and ensure comparability with the ORAL Surveillance trial results.[8 10] The RCT-duplicate cohort was restricted to patients at least 50 years of age (65 in Medicare) with at least one methotrexate dispensation in 6 months prior to cohort entry date. This cohort was also restricted to patients with at least one CV risk factor including history of smoking, hypertension, dyslipidaemia, diabetes mellitus, ischaemic heart disease or family history of ischaemic heart disease. Patients hospitalised with infections in the 30 days prior to cohort entry date and pregnant patients were excluded from the RCT-duplicate cohort.

Exposure and outcome definition

We used an as-treated exposure definition whereby patients were followed from treatment initiation for study outcomes until treatment discontinuation or switch, insurance disenrollment, death, or end of the study period, whichever occurred first. The primary endpoint was defined as a composite CV outcome consisting of hospitalisations for myocardial infarction (MI) or stroke. Patients were followed for CV outcomes on the day after the cohort entry date (online supplemental figure 1). Individual CV outcomes were also examined independently as secondary outcomes including MI, stroke, heart failure hospitalisation and coronary revascularisation. We also examined the risk of all-cause mortality as an additional secondary outcome. Finally, we examined the risk of herpes zoster as a positive control outcome as previous studies have established an increased risk of herpes zoster with tofacitinib.[15 16]

Covariate assessment

We assessed 76 potential confounders (75 in MarketScan) during the baseline covariate assessment period defined as the 365 days prior to treatment initiation (full list of covariates are included in online supplemental methods).

Statistical analysis

Descriptive statistics were used to summarise baseline characteristics for each study cohort. Crude incidence rates and corresponding 95% CIs were reported for each study outcome. Propensity score (PS) fine stratification weighting was used to account for measured confounders in this study (details outlined in online supplemental methods).[17] Standardised differences (%) were used to assess the balance in individual covariates between two treatment groups before and after PS fine-stratification weighting.[18 19] Cox proportional hazards model were used to estimate HRs and corresponding 95% CIs accounting for potential confounders using PS fine stratification weights and using an as-treated exposure definition in the primary analysis. Robust variance estimation was used to calculate 95% CI to account for weighting. We also assessed crude and weighted difference in rates and corresponding 95% CI when comparing tofacitinib with TNFI using Poisson regression. Effect estimates were pooled across three databases using fixed effects model with inverse variance weighting. We examined cumulative incidence of composite CV outcomes and the corresponding 95% CI separately for each treatment group. We used the Aetion Evidence Platform for cohort construction.[20] Analyses were conducted using SAS V.9.4 (SAS Institute) and R (R Foundation for Statistical Computing, Vienna, Austria).

Secondary and sensitivity analyses

Prespecified subgroup analyses were conducted based on age (≤65 and >65), sex and baseline CVD (RWE cohorts only). In addition, we examined the risk of CV outcomes by stratifying by unique number of previous agents of bDMARDs (ie, 0 vs ≥1). Secondary analysis was also conducted by using an intention-to-treat exposure definition whereby patients were censored 365

days after initiation of treatment with tofacitinib or TNFI. We also conducted 1:1 PS matching where each patient initiating tofacitinib was matched with a patient initiating TNFI using nearest neighbour greedy matching without replacement using a calliper of 0.025 on the natural scale of the PS.[21 22] Finally, sensitivity analyses were conducted by restricting the TNFI comparator group in RWE and RCT-duplicate cohorts to only adalimumab and etanercept users, the specific TNFI which were the comparator in the ORAL Surveillance trial.[9 10]

RESULTS

RWE cohort

Study population

The Consort diagrams for construction of the RWE and RCT-duplicate cohorts are outlined in online supplemental tables 1–6. In RWE cohort, 28 568, 34 083 and 39 612 patients who met the inclusion and exclusion criteria were identified from Optum, MarketScan and Medicare, respectively, of whom 13.2%, 15.6% and 9.5% initiated treatment on tofacitinib (online supplemental table 7). The mean age, in years, comparing tofacitinib and TNFI users was 56.8 vs 54.6 in Optum, 54.7 vs 52.7 in MarketScan, and 72.1 vs 72.2 in Medicare. The majority of patients in RWE cohort were female across the three databases (77%–79%). The prevalence of CVD risk factors and previous use of comedications was slightly higher in tofacitinib users compared with TNFI users (online supplemental table 7).

In RWE cohort, 13% of patients in Optum, 10% in MarketScan, and 31% in Medicare had a history of CVD. There were no discernable differences across most markers of healthcare utilisation when comparing tofacitinib and TNFI users (online supplemental table 7). Overall, PS fine stratification achieved excellent covariate balance with standardised differences close to zero across all covariates (table 1, online supplemental table 8).

Primary outcome

The crude incidence rates of the primary CV endpoint per 100 person-years (95% CI) for tofacitinib and TNFI users were 0.73 (0.47 to 1.09) and 0.61 (0.51 to 0.72) in Optum, 0.75 (0.52 to 1.05) and 0.52 (0.44 to 0.61) in MarketScan, and 2.14 (1.66 to 2.70) and 1.86 (1.71 to 2.02) in Medicare (table 2).

In the primary analysis, the pooled weighted HR (95% CI) for CV outcomes when comparing tofacitinib with TNFI was 1.01 (0.83 to 1.23) with weighted rate difference (95% CI) corresponding to 0.02 (−0.19 to 0.23) CV events per 100 person-years (figure 1 and online supplemental table 9). Correspondingly, there was no differences in cumulative incidence of composite CV outcomes when comparing tofacitinib with TNFI in any of the three databases (online supplemental figure 2). Among tofacitinib users, the median (IQR) months to CV events was 6.9 (2.9–16.3) in Optum, 5.1 (2.0–12.3) in MarketScan and 6.0 (2.0–13.4) in Medicare. Among TNFI users, the median (IQR) months to CV events was 7.5 (2.7–17.5) in Optum, 6.1 (2.5–11.7) in MarketScan and 6.3 (2.4–15.1) in Medicare.

In subgroup analyses, the pooled weighted HR (95% CI) was 1.27 (0.95 to 1.70) and 0.81 (0.61 to 1.07) among patients with and without history of CVD respectively (figure 2 and online supplemental table 9). The pooled weighted HR (95% CI) among patients ≤65 years of age was 1.00 (0.66 to 1.50) and 1.05 (0.84 to 1.33) for patient aged more than 65 years. No association was observed across other subgroups including among males (pooled weighted HR 1.05, 95% CI 0.70 to 1.56), females (pooled weighted HR 0.97, 95% CI 0.77 to 1.23), patients with previous use of bDMARDs (pooled weighted HR 1.06, 95% CI 0.79 to 1.40), and patients without previous use of bDMARDs (pooled weighted HR 1.02, 95% CI 0.77 to 1.35). Consistent results were observed across other sensitivity and secondary analyses including PS matching, intention-to-treat exposure definition, and restriction of the TNFI comparator to adalimumab and etanercept users (online supplemental table 9).

Secondary outcomes

For individual CV outcomes, the pooled weighted HR (95% CI) was 1.04 (0.82 to 1.33) for MI, 0.93 (0.66 to 1.31) for stroke, 1.07 (0.79 to 1.46) for heart failure hospitalisation and 1.04 (0.78 to 1.40) for coronary revascularisation (online supplemental table 10) when comparing tofacitinib users with TNFI users. The pooled weighted HR (95% CI) was 1.20 (0.98 to 1.46) for all-cause mortality. For the positive control outcome, we successfully replicated the known association between tofacitinib and risk of herpes zoster (pooled weighted HR 1.98, 95% CI 1.78 to 2.19).

RCT-duplicate cohort

Study population

In the RCT-duplicate cohort, 6878, 8071 and 20 121 patients were identified from Optum, MarketScan and Medicare, respectively, of whom 11.6%, 14.3% and 7.7% initiated treatment with tofacitinib (online supplemental table 11). Overall, PS fine stratification weighting achieved excellent covariate balance in this study population with standardised differences close to zero for all covariates (online supplemental table 12).

Primary outcome

The crude incidence rates of the primary CV endpoint per 100 person-years (95% CI) for tofacitinib and TNFI users were 1.33 (0.64 to 2.45) and 0.94 (0.71 to 1.23) in Optum, 1.22 (0.65 to 2.08) and 0.80 (0.60 to 1.04) in MarketScan, and 2.39 (1.64 to 3.38) and 1.78 (1.58 to 2.00) in Medicare (table 2). In the primary analysis, the pooled weighted HR (95% CI) for primary CV outcome was 1.24 (0.90 to 1.69) corresponding to a pooled weighted rate difference (95% CI) of 0.28 (−0.24 to 0.80) CV events per 100 person-years when comparing tofacitinib users with TNFI users (figure 1 and online supplemental table 13). The cumulative incidence of CV outcomes was similar when comparing with tofacitinib with TNFI users in Optum and MarketScan but was slightly higher among tofacitinib users in Medicare, although with wide CIs for these analyses (online supplemental figure 3). The median months (IQR) to CV events among tofacitinib users was 6.9 (2.6–14.2) in Optum, 6.0 (2.8–11.8) in MarketScan and 5.2 (1.7–12.4) in Medicare. Among TNFI users, the median (IQR) months to CV events was 6.9 (3.0–11.0) in Optum, 7.1 (2.8–12.5) in MarketScan and 6.8 (2.2–15.8) in Medicare. In sensitivity analysis restricting comparator to adalimumab and etanercept (online supplemental table 13), the pooled weighted HR (95%) CI for primary CV outcome was 1.32 (0.94 to 1.86).

DISCUSSION

Overall, in this large population-based study, tofacitinib in comparison with TNFI was not associated with risk of composite CV outcome in patients with RA treated in real-world settings (pooled weighted HR 1.01, 95% CI 0.83 to 1.23). Results from the RCT-duplicate cohort were consistent with those reported from the ORAL surveillance trial (pooled weighted HR 1.24, 95% CI 0.90 to 1.69 vs trial: 1.33, 95% CI 0.91 to 1.94).[8 10] An increased risk of CV outcomes was also observed among

Table 1 Select baseline characteristics of RWE RA patients initiating tofacitinib or TNFi after propensity score fine stratification weighting

Variable	Optum			MarketScan*			Medicare		
	Tofacitinib (N=3761)	TNFI (N=24 688)	SD (%)	Tofacitinib (N=5298)	TNFI (N=28 727)	SD (%)	Tofacitinib (N=3782)	TNFI (N=35 816)	SD (%)
Demographics									
Age; mean (std)	56.8 (12.5)	57.1 (13.2)	−2.6	54.7 (11.5)	55.0 (12.0)	−1.9	72.1 (5.6)	72.2 (5.6)	−1.3
Female gender; n (%)	3043 (80.9)	20 046 (81.2)	−0.7	4333 (81.8)	23 503 (81.8)	−0.1	3134 (82.9)	29 819 (83.3)	−1.0
White race; n (%)	2395 (63.7)	15 691 (63.6)	0.3	–	–	–	3026 (80.0)	28 449 (79.4)	1.4
Black race; n (%)	412 (11.0)	2737 (11.1)	−0.4	–	–	–	410 (10.8)	4051 (11.3)	−1.5
Asian race; n (%)	103 (2.7)	643 (2.6)	0.8	–	–	–	85 (2.2)	810 (2.3)	−0.1
Hispanic race; n (%)	471 (12.5)	3127 (12.7)	−0.4	–	–	–	126 (3.3)	1224 (3.4)	−0.5
RA related variables									
No of unique bDMARDs; mean (std)	1.6 (0.7)	1.6 (0.7)	2.4	1.8 (0.8)	1.8 (0.8)	1.6	1.6 (0.7)	1.6 (0.7)	2.2
Non-biologic DMARDs									
No of distinct csDMARDs; mean (std)	1.0 (0.8)	1.0 (0.8)	0.3	1.0 (0.8)	1.0 (0.8)	1.8	1.1 (0.8)	1.1 (0.8)	0.8
Any csDMARD use; n (%)	2723 (72.4)	17 851 (72.3)	0.2	3989 (75.3)	21 451 (74.7)	1.4	2889 (76.4)	27 253 (76.1)	0.7
Methotrexate; n (%)	1731 (46.0)	11 244 (45.5)	1.0	2722 (51.4)	14 582 (50.8)	1.2	1954 (51.7)	18 239 (50.9)	1.5
Hydroxychloroquine; n (%)	933 (24.8)	6143 (24.9)	−0.2	1254 (23.7)	6639 (23.1)	1.3	950 (25.1)	8915 (24.9)	0.5
Leflunomide; n (%)	799 (21.2)	5273 (21.4)	−0.3	1065 (20.1)	5756 (20.0)	0.2	828 (21.9)	7935 (22.2)	−0.6
Sulfasalazine; n (%)	388 (10.3)	2558 (10.4)	−0.1	491 (9.3)	2604 (9.1)	0.7	418 (11.1)	3988 (11.1)	−0.3
Glucocorticoid use									
Prior use of oral glucocorticoids (365 days); n (%)	2814 (74.8)	18 489 (74.9)	−0.2	3896 (73.5)	21 185 (73.7)	−0.5	2846 (75.3)	26 944 (75.2)	0.1
Recent use of oral glucocorticoids (60 days); n (%)	1898 (50.5)	12 458 (50.5)	0.0	2625 (49.5)	14 274 (49.7)	−0.3	2115 (55.9)	20 072 (56.0)	−0.2
Cumulative dose of oral steroids in mg; mean (std)	934.5 (1,485.5)	935.6 (5,973.1)	0.0	1952.8 (25,666.3)	2094 (26,335.2)	−0.5	1024.5 (1,195.2)	1019.6 (1,279.5)	0.4
CVD risk factors									
Obesity; n (%)	882 (23.5)	5876 (23.8)	−0.8	810 (15.3)	4392 (15.3)	0.0	581 (15.4)	5446 (15.2)	0.4
Smoking; n (%)	749 (19.9)	4925 (20.0)	−0.1	465 (8.8)	2566 (8.9)	−0.6	972 (25.7)	9180 (25.6)	0.2
Atrial fibrillation; n (%)	154 (4.1)	1038 (4.2)	−0.6	140 (2.6)	752 (2.6)	0.1	397 (10.5)	3723 (10.4)	0.3
Coronary artery disease; n (%)	381 (10.1)	2564 (10.4)	−0.8	425 (8.0)	2394 (8.3)	−1.1	904 (23.9)	8477 (23.7)	0.5
Type 2 diabetes mellitus; n (%)	805 (21.4)	5353 (21.7)	−0.7	835 (15.8)	4563 (15.9)	−0.3	1162 (30.7)	10 918 (30.5)	0.5
Heart failure; n (%)	192 (5.1)	1324 (5.4)	−1.2	175 (3.3)	960 (3.3)	−0.2	450 (11.9)	4267 (11.9)	0.0
Hypertension; n (%)	1966 (52.3)	13 075 (53.0)	−1.4	2355 (44.5)	12 922 (45.0)	−1.1	3110 (82.2)	29 417 (82.1)	0.3
Hyperlipidaemia; n (%)	1619 (43.0)	10 706 (43.4)	−0.6	2002 (37.8)	10 937 (38.1)	−0.6	2569 (67.9)	24 187 (67.5)	0.8
Stroke or transient ischaemic attack; n (%)	92 (2.4)	605 (2.5)	0.0	113 (2.1)	620 (2.2)	−0.2	134 (3.5)	1255 (3.5)	0.2
Peripheral vascular disease; n (%)	163 (4.3)	1103 (4.5)	−0.6	141 (2.7)	776 (2.7)	−0.3	442 (11.7)	4166 (11.6)	0.2
Venous thromboembolism; n (%)	102 (2.7)	699 (2.8)	−0.7	141 (2.7)	765 (2.7)	0.0	103 (2.7)	996 (2.8)	−0.4
Other comorbidities									
Chronic liver disease; n (%)	273 (7.3)	1792 (7.3)	0.0	315 (5.9)	1696 (5.9)	0.2	317 (8.4)	2985 (8.3)	0.2
Chronic kidney disease (Stage 3+); n (%)	212 (5.6)	1428 (5.8)	−0.6	168 (3.2)	926 (3.2)	−0.3	442 (11.7)	4207 (11.7)	−0.2
COPD; n (%)	599 (15.9)	3992 (16.2)	−0.7	629 (11.9)	3454 (12.0)	−0.5	1041 (27.5)	9955 (27.8)	−0.6
Inflammatory bowel disease; n (%)	63 (1.7)	415 (1.7)	0.0	68 (1.3)	353 (1.2)	0.5	50 (1.3)	461 (1.3)	0.3
Psoriasis; n (%)	170 (4.5)	1100 (4.5)	0.3	169 (3.2)	885 (3.1)	0.6	119 (3.1)	1028 (2.9)	1.6
Cancer (excluding NMSC); n (%)	484 (12.9)	3267 (13.2)	−1.1	692 (13.1)	3783 (13.2)	−0.3	789 (20.9)	7438 (20.8)	0.2
Combined Comorbidity Index; mean (std)	1.2 (2.0)	1.2 (2.0)	−0.8	0.7 (1.5)	0.7 (1.5)	−0.7	1.8 (2.4)	1.9 (2.4)	−0.4
Frailty score; mean (std)	0.2 (0.0)	0.2 (0.0)	−0.8	0.1 (0.0)	0.1 (0.0)	−1.5	0.2 (0.0)	0.2 (0.0)	0.0

Full Tables describing all patient characteristics before and after PS-weighting are provided in online supplemental material.
*Data for race are not available in MarketScan.
bDMARD, biological disease-modifying antirheumatic drugs; COPD, Chronic obstructive pulmonary disease; CRP, C reactive protein; csDMARDs, conventional synthetic DMARDs; CVD, cardiovascular disease; NMSC, non-melanoma skin cancer; RA, rheumatoid arthritis; RWE, real-world evidence; SD, standardized difference; std, standard deviation; TNFI, tumour necrosis factor inhibitors.

RWE patients with history of CVD (pooled weighted HR 1.27, 95% CI 0.95 to 1.70) but not those without history of CVD (pooled weighted HR 0.81, 95% CI 0.61 to 1.07).

The findings from previous studies examining the association between tofacitinib and CV outcomes have been discordant. Recent reports from the ORAL Surveillance trial have indicated that both 5 mg and 10 mg two times per day dose of tofacitinib, in comparison with TNFI, were associated with increased risk of MACE (HR 1.24, 95% CI 0.81 to 1.91 and HR 1.43, 95% CI 0.94 to 2.18, respectively).[8 10] This trial consisted 4362 patients who were at least 50 years of age, with one at least one risk factor for CVD, and with a background of treatment with methotrexate.[9 10] Results from a recent meta-analysis of RCTs, excluding ORAL surveillance, were inconclusive for the association between tofacitinib and CV risk in patients with RA (OR 1.29, 95% CI 0.40 to 4.13) or chronic plaque psoriasis (OR 3.61, 95% CI 0.71

Table 2 Incidence rate, crude HR, and corresponding 95% CIs for the primary composite cardiovascular outcome in RWE and RCT-duplicate cohort of rheumatoid arthritis patients initiating treatment with tofacitinib or TNFi

Data source	Exposure group	Sample size	Events	Total person years of follow-up	Crude incidence rate (95% CI)*	Crude incidence rate difference (95% CI)*	Crude HR (95% CI)
RWE Cohort							
Optum	TNFI	24 805	143	23 458	0.61 (0.51 to 0.72)	Ref	Ref
	Tofacitinib	3763	24	3273	0.73 (0.47 to 1.09)	0.12 (-0.19 to 0.43)	1.21 (0.78 to 1.86)
MarketScan	TNFI	28 776	141	27 257	0.52 (0.44 to 0.61)	Ref	Ref
	Tofacitinib	5307	35	4655	0.75 (0.52 to 1.05)	0.23 (-0.03 to 0.50)	1.44 (0.99 to 2.09)
Medicare	TNFI	35 830	562	30 277	1.86 (1.71 to 2.02)	Ref	Ref
	Tofacitinib	3782	69	3229	2.14 (1.66 to 2.70)	0.28 (-0.25 to 0.81)	1.15 (0.89 to 1.48)
Pooled	TNFI	89 411	846	80 992	1.24 (1.16 to 1.33)	Ref	Ref
	Tofacitinib	12 852	128	11 157	1.31 (1.10 to 1.56)	0.20 (0.01 to 0.39)	1.23 (1.02 to 1.48)
RCT-duplicate cohort							
Optum	TNFI	6077	56	5932	0.94 (0.71 to 1.23)	Ref	Ref
	Tofacitinib	801	10	752	1.33 (0.64 to 2.45)	0.39 (-0.47 to 1.25)	1.43 (0.73 to 2.81)
MarketScan	TNFI	6920	55	6857	0.80 (0.60 to 1.04)	Ref	Ref
	Tofacitinib	1151	13	1069	1.22 (0.65 to 2.08)	0.41 (-0.28 to 1.11)	1.50 (0.82 to 2.74)
Medicare	TNFI	18 576	289	16 241	1.78 (1.58 to 2.00)	Ref	Ref
	Tofacitinib	1545	32	1338	2.39 (1.64 to 3.38)	0.61 (-0.24 to 1.47)	1.35 (0.93 to 1.94)
Pooled	TNFI	31 573	400	29 030	1.46 (1.32 to 1.61)	Ref	Ref
	Tofacitinib	3497	55	3159	1.83 (1.41 to 2.39)	0.46 (0.01 to 0.92)	1.39 (1.05 to 1.85)

All estimates were pooled using fixed effects models with inverse variance weighting.
*Per 100 person-years.
CI, confidence interval; HR, hazard ratio; RCT, randomised controlled trial; RWE, real world evidence; TNFI, tumour necrosis factor inhibitors.

to 18.43) due to low event rates.[23] In contrast, among patients enrolled in the CORRONA RA registry in the USA, tofacitinib, in comparison with bDMARDs (including TNFI and non-TNFI biologics), was not associated with an increased risk of MACE which was defined as MI, stroke, transient ischaemic attack or CV death (HR 0.61, 95% CI 0.34 to 1.06).[24] Our results suggest that the association between tofacitinib and CV outcomes may be modified by baseline CV risk. In patients from our RWE cohort who had no underlying CV risk factors or history (87% of patients in Optum, 90% in MarketScan and 69% in Medicare), we noted no detectable impact of tofacitinib treatment on risk of adverse CV outcomes. However, among patients with CV risk factors or history, estimates consistently suggested a potentially elevated risk. We recommend continuing research to better understand risk–benefit trade-offs of this important treatment option in a wide range of patients with RA.

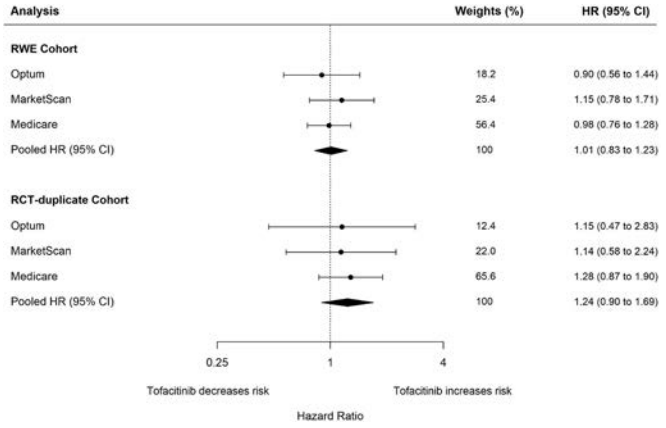

Figure 1 Forest plot of propensity score fine stratification weighted HRs and corresponding 95% CIs for composite cardiovascular outcomes when comparing tofacitinib with tumour necrosis factor inhibitors in patients with rheumatoid arthritis in RWE cohort (top panel) and RCT-duplicate cohort (bottom panel). RCT, randomised controlled trial; RWE, real-world evidence.

Overall, there is no known direct mechanism that would explain a detrimental effect of tofacitinib on risk of CV outcomes. In phase II and III trials, both doses of tofacitinib (5 mg or 10 mg)

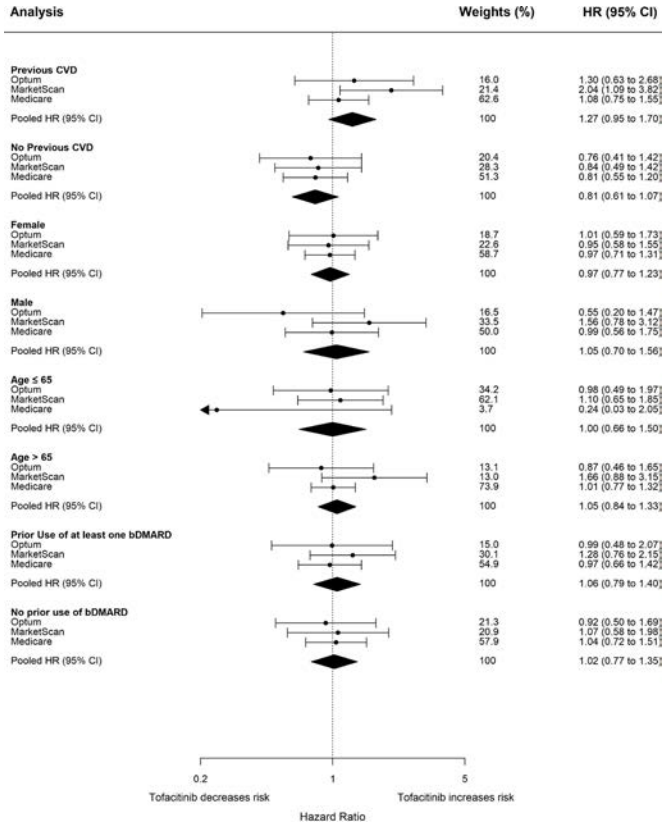

Figure 2 Forest plot of propensity score fine stratification weighted HRs and corresponding 95% CIs for composite cardiovascular outcomes for subgroup analyses in RWE study cohort. bDMARDs, biological disease-modifying antirheumatic drugs; CVD, cardiovascular disease; RWE, real-world evidence.

either as monotherapy or in combination with non-bDMARDs were associated with 15% to 20% increase in low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C levels) when comparing 4 weeks after treatment initiation with baseline. The changes in LDL-C and HDL-C levels persisted 12 months after treatment initiation.[25] However, the levels of the ratio of total-cholesterol: HDL-C and LDL-C: HDL-C levels, which are more reliable predictors of CV events, did not change.[25] In another study with 46 patients with RA, tofacitinib was not associated with changes in carotid intima–media thickness when comparing 54 weeks after treatment initiation with baseline (1.09±0.69 and 1.08±0.78 mm, respectively).[26] Additional mechanistic studies will be required in light of potential increased risk of CV outcomes associated with tofacitinib in ORAL Surveillance trial.

This study has strengths and limitations. First, we conducted a large multidatabase population-based studies with more than 102 000 patients, a sample size larger than the ORAL Surveillance trial and CORRONA RA registry study in the USA.[8 10 24] Second, we comprehensively assessed the risk of individual CV outcomes including MI, stroke, heart failure and coronary revascularisation. Third, we employed a new user design active comparator design to control for confounding by disease severity and circumvent prevalent-user bias.[11] Fourth, we calibrated our results using the RCT-duplicate cohort to assess the validity of the study and ensure that are results were comparable with those of the ORAL surveillance postmarketing trial.[8 10] Fifth, we found an increased risk of herpes zoster infection which was included as a positive control outcome, consistent with previous studies.[15 16] Finally, the study protocol was preregistered prior to conducting our study.[12] Our study has some limitations. First, residual confounding by factors not captured in administrative claims including RA activity is possible. However, we used an active comparator group (ie, TNF inhibitors) and adjusted for 76 confounders (75 in MarketScan) including multiple variables that may serve as proxies for RA disease severity. Reassuringly, a recent study using the CORRONA RA registry, a prospective disease-based registry inclusive of 50 605 patients with RA across 177 private and academic practices in the USA, demonstrated that patients with RA who are treated with tofacitinib are comparable to patients treated with bDMARDs in regards to RA-related variables including clinical disease activity index.[24] In addition, we observed approximately equal distribution in time to CV events throughout follow-up after treatment initiation among tofacitinib and TNFI users in RWE and RCT-duplicate cohorts. Second, exposure misclassification is possible due to incomplete adherence to study drugs. To minimise exposure misclassification, we implemented an as-treated exposure definition where the occurrence of study outcomes was assessed while patients were on treatment. Finally, we could not assess the risk of CV outcomes with newer JAK inhibitors including baricitinib and upadacitinib, and thus, additional studies will be required to examine the risk of CV outcomes with these newer agents.

Overall, in this multidatabase population-based study, we did not find evidence for an increased risk of CV outcomes with tofacitinib, in comparison with TNFI, among patients with RA treated in the real-world setting. However, concordant with results from ORAL Surveillance safety trial, tofacitinib, in comparison with TNFI, was associated with an elevated risk of CV outcomes, though statistically non-significant, in patients with RA with CV risk factors or a history of CVD. Thus, an elevated risk of CV outcomes cannot be ruled out in patients with CV risk factors or history of CVD.

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Contributors RJD had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: RJD, SCK and FK-K. Analysis of data: RJD, FK-K and SBL. Interpretation of data and drafting of the manuscript: all authors. RJD acts as guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data and controlled the decision to publish.

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Competing interests RJD has received research grants to the Brigham and Women's Hospital from Bayer, Novartis, and Vertex for unrelated projects. SCK has received research grants to the Brigham and Women's Hospital from Roche/Genentech, Pfizer, Bristol-Myers Squibb, Roche, and AbbVie for unrelated studies. All other authors have no conflict of interests to disclose.

Patient consent for publication Not applicable.

Ethics approval The study protocol received approval (IRB #2011P002580-207) from the Institutional Review Board of Brigham and Women's Hospital (Boston, Massachusetts).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The databases used in the study can be accessed through a license with MarketScan, Optum, and Medicare. No additional data are available from the authors.

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TRANSLATIONAL SCIENCE

Ageing and interferon gamma response drive the phenotype of neutrophils in the inflamed joint

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ABSTRACT

Objective Neutrophils are typically the most abundant leucocyte in arthritic synovial fluid. We sought to understand changes that occur in neutrophils as they migrate from blood to joint.

Methods We performed RNA sequencing of neutrophils from healthy human blood, arthritic blood and arthritic synovial fluid, comparing transcriptional signatures with those from murine K/BxN serum transfer arthritis. We employed mass cytometry to quantify protein expression and sought to reproduce the synovial fluid phenotype ex vivo in cultured healthy blood neutrophils.

Results Blood neutrophils from healthy donors and patients with active arthritis showed largely similar transcriptional signatures. By contrast, synovial fluid neutrophils exhibited more than 1600 differentially expressed genes. Gene signatures identified a prominent response to interferon gamma (IFN-γ), as well as to tumour necrosis factor, interleukin-6 and hypoxia, in both humans and mice. Mass cytometry confirmed that healthy and arthritic donor blood neutrophils are largely indistinguishable but revealed a range of neutrophil phenotypes in synovial fluid defined by downregulation of CXCR1 and upregulation of FcγRI, HLA-DR, PD-L1, ICAM-1 and CXCR4. Reproduction of key elements of this signature in cultured blood neutrophils required both IFN-γ and prolonged culture.

Conclusions Circulating neutrophils from patients with arthritis resemble those from healthy controls, but joint fluid cells exhibit a network of changes, conserved across species, that implicate IFN-γ response and ageing as complementary drivers of the synovial fluid neutrophil phenotype.

Key messages

What is already known about this subject?

⇒ Neutrophils are central in the effector phase of inflammatory arthritis, but their phenotypical heterogeneity in inflamed synovial fluid is poorly understood.

What does this study add?

⇒ RNA sequencing and mass cytometry identify a hallmark phenotype of neutrophils in synovial fluid consisting of upregulated ICAM-1, HLA-DR, PD-L1, Fc receptors and CXCR4.

⇒ Transcriptomics highlight an interferon gamma (IFN-γ) response signature conserved across humans and mice.

⇒ In vitro experiments implicate IFN-γ and ageing as complementary factors orchestrating the synovial fluid neutrophil phenotype.

How might this impact on clinical practice or future developments?

⇒ Understanding the specific features of neutrophils in the arthritic joint may disclose opportunities for safe therapeutic targeting of this lineage.

INTRODUCTION

Inflammatory arthritis encompasses a broad spectrum of diseases affecting adults and children.[1] The pathogenesis of non-infectious arthritis is correspondingly varied, with upstream mechanisms that include autoantibodies, T cells, autoinflammatory mechanisms and crystals.[2] Despite this remarkable pathogenic diversity, a ubiquitous feature of arthritic joint fluid is an abundance of neutrophils, a canonical innate immune effector cell required for immune defence but also for many inflammatory diseases.

Compelling evidence confirms that neutrophils are key pathogenic contributors in arthritis. Neutrophils from human joints exhibit altered surface markers and function consistent with activation.[3–7] Synovial neutrophils elaborate proinflammatory factors such as interleukin (IL)-1, leucotriene B4, citrullinated peptides and neutrophil extracellular traps.[8–11] Neutrophils activated by adherent immune complexes degrade articular cartilage.[12] Finally, mice with defects specific to the neutrophil compartment—for example, depleted of neutrophils, congenitally deficient in neutrophils, with neutrophils lacking key effector molecules, or subject to neutrophil migratory blockade—exhibit dense resistance to experimental arthritis.[11 13–17] Therefore, understanding the phenotype of synovial fluid neutrophils is essential to understanding the biology of arthritis and may reveal novel opportunities for therapeutic intervention.[18]

Advances in cellular characterisation offer new ways to understand neutrophils. Transcriptomic analysis provides a hypothesis-independent examination of the activity of cells at the gene expression level, informing the relationships between populations of cells. For example, studies using single-cell RNA sequencing (scRNAseq) recently established that murine neutrophils represent a single lineage, differentiating along a developmental continuum termed 'neutrotime', rather than a branched network of committed subtypes.[19] Indeed, ageing is well recognised as a modulator of neutrophil phenotype and function.[20 21] Importantly, however, the relationship between a neutrophil's transcriptome and its surface protein signature varies markedly with context.[19] For example, neutrophil activation results in rapid mobilisation of the surface integrin CD11b from an intracellular pool and cleavage-mediated loss of the surface selectin CD62L.[22] Mass cytometry (cytometry by time of flight (CyTOF)) permits simultaneous determination of dozens of surface and intracellular markers in each cell, although restricted by investigator choice as to the markers most likely to prove informative.[23]

To understand the changes that occur in neutrophils as they enter the inflamed joint, we applied low-input RNA sequencing (RNAseq) to purified neutrophils, sorting cells by a known dichotomous surface marker of undetermined function, CD177, to eliminate potential confounding by variation in the $CD177^{pos}$ neutrophil fraction within the population.[24] We compared human neutrophils with scRNAseq transcriptome data from murine neutrophils, both circulating and from autoantibody-mediated neutrophil-driven K/BxN serum transfer arthritis.[25] We employed CyTOF to define markers of neutrophil differentiation and function, followed by confirmatory in vitro studies using flow cytometry. We establish that blood neutrophils from healthy and arthritic donors are largely similar but that synovial fluid neutrophils differ markedly from blood neutrophils in a manner that implicates both interferon gamma (IFN-γ) response and cell ageing in the resulting phenotype.

METHODS

Subject characteristics and materials and methods are available in the online supplemental materials.

RESULTS

Transcriptomic characterisation of circulating neutrophils

We performed low-input RNAseq on blood neutrophils from 15 healthy donors and 16 individuals with inflammatory arthritis (rheumatoid arthritis, juvenile idiopathic arthritis and undifferentiated inflammatory arthritis (online supplemental table 1), calculating Pearson correlation coefficients between samples based on the expression of all genes. Hierarchical clustering of these correlation coefficients revealed no separation by disease state, suggesting little divergence of transcriptional phenotype (figure 1A). At false discovery rate (FDR) of 0.05 (indicated by red line), blood neutrophils from healthy and arthritic donors differed in only three genes: *DNAJB9* (DnaJ heat shock protein family (Hsp40) member B9), *DDIT4* (DNA damage inducible transcript 4) and *SCO2* (synthesis of cytochrome C oxidase 2), all modestly upregulated in arthritis (figure 1B,C).

Synovial fluid neutrophils display an IFN-γ response

We performed the same analysis in 16 paired contemporaneous peripheral blood and synovial fluid samples from patients with active arthritis requiring therapeutic joint aspiration. Hierarchical clustering revealed separation into two groups as a function of location (figure 2A). At $|\log \text{fold change}| \geq 1$ and FDR 0.05, 1657 genes were differentially expressed, of which 939 were downregulated and 718 upregulated (figure 2B).

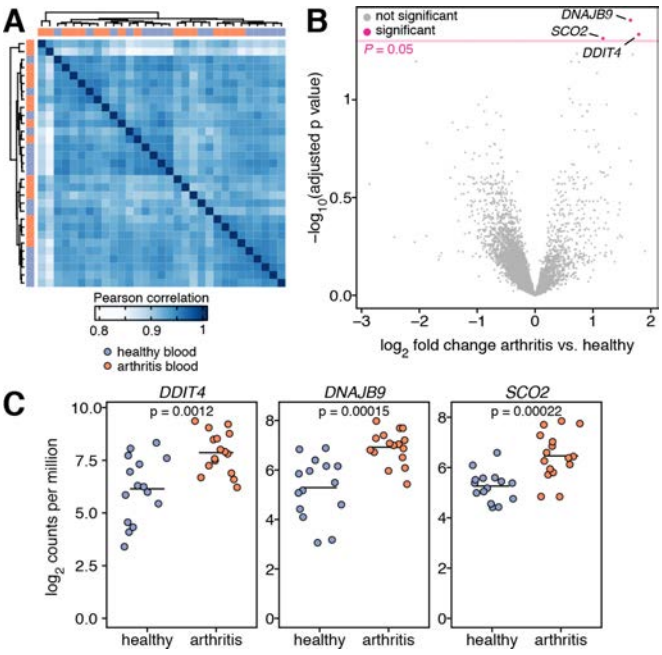

Figure 1 Transcriptomic similarity of blood neutrophils from healthy controls and patients with inflammatory arthritis. (A) Hierarchical clustering of Pearson correlation coefficients between individual blood samples based on the expression of all genes reveals complete overlap between the two groups. (B) Volcano plot of differentially expressed genes (at FDR 0.05) between blood neutrophils from healthy and arthritic donors. (C) *DNAJB9*, *DDIT4* and *SCO2* are overexpressed in blood of patients with inflammatory arthritis compared with healthy controls. n=15, healthy controls; n=16, patients with arthritis.

To understand these genes in terms of functional programmes, we employed gene set enrichment analysis using the established 50 hallmark gene sets together with 292 gene sets from Biocarta. Signatures of several inflammatory cytokines were detected and included IL-1, IL-17, IL-12, IL-2, IL-6, interferon alpha, as well as response to hypoxia (figure 2C). However, the most prominent gene set in synovial fluid neutrophils was IFN-γ response (figure 2C,D). Analysis of genes upregulated in response to IFN-γ (HALLMARK_INTERFERON_GAMMA_RESPONSE) revealed that 93 of 175 expressed IFN-γ target genes were highly induced in synovial fluid neutrophils, including the class II molecules *CD74*, *HLA-DMA*, *HLA-DRB1* and *HLA-DQA1*; *CD274* (encoding PD-L1); and *FCGR1A* (encoding CD64, the high-affinity IgG receptor FcγRI) (figure 2E). These observations show that phenotypical deviation of neutrophils in arthritis is primarily in the joints rather than in the circulation, at least at the transcriptional level, and suggest a prominent role for IFN-γ in driving the phenotype of synovial fluid neutrophils.

Conserved responses of human and murine neutrophils in inflammatory arthritis

Neutrophils are indispensable for onset and perpetuation of joint inflammation in mice.[8–11 14–16] To test whether the transcriptional changes we observed in human synovial neutrophils are conserved across species, we compared our human dataset to a microarray-based transcriptional atlas of neutrophils from the blood of healthy mice and joints of mice undergoing K/BxN serum transfer arthritis.[25] We restricted the combined dataset

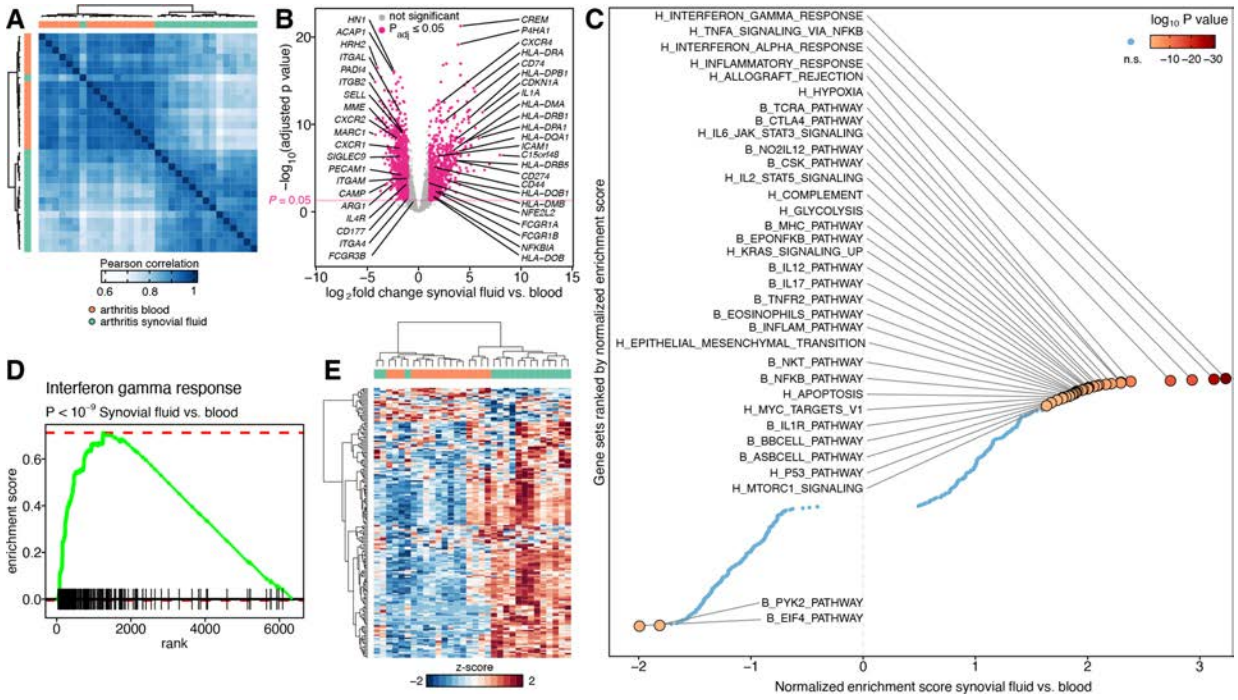

Figure 2 Synovial fluid neutrophils are enriched for IFN-γ response genes. (A) Hierarchical clustering of Pearson correlation coefficients between paired peripheral blood and synovial fluid samples based on the expression of all genes shows strong separation based on tissue. (B) 1657/6350 genes are differentially expressed at $\log_2$ fold change ≥1 and FDR of 0.05 between peripheral blood and synovial fluid neutrophils. (C) Gene set enrichment analysis of differentially expressed genes in synovial fluid versus blood neutrophils. (D) Enrichment plot of the IFN-γ response signature in synovial fluid neutrophils. (E) Expression heatmap of IFN-γ response genes in synovial fluid neutrophils reveals strong separation between blood and synovial fluid. n=16, paired blood and synovial fluid inflammatory arthritis samples. IFN-γ, interferon gamma.

to 5520 one-to-one gene orthologues according to ENSEMBL V.100.[26] Of genes with orthologues significantly upregulated in human (578) and murine (226) synovial fluid neutrophils, 97 were shared across species, far more than expected by chance (95% CI for chance overlap 16–34 genes as defined by random resampling 20 000 times, $p=2.7\times10^{-7}$; figure 3A). Similarly, downregulated genes across human (774) and mouse (174) neutrophils in synovial fluid shared significant overlap with 75 genes, compared with 23–41 expected by chance ($p=1.3\times10^{-11}$, figure 3A). In murine synovial fluid neutrophils, enhanced expression was observed in IFN-γ target genes including *CD274* (encoding PD-L1) and the MHC class II gene *HLADQB1*; indeed an IFN-γ signature was one of the key functional patterns observed, with highly skewed representation of IFN-γ response genes (adjusted $p<0.001$, figure 3B,C). These findings establish that gene expression changes, including an IFN-γ response signature, are shared by human and murine synovial fluid neutrophils.

CyTOF confirms joint-specific activation of human neutrophils in inflammatory arthritis

We created a custom CyTOF panel containing 39 human surface and intracellular markers related to neutrophil activation, chemokine receptors, antigen presentation, adhesion factors and costimulatory molecules (online supplemental methods). CyTOF was performed in 33 samples: 9 healthy volunteer donors, 8 blood samples from patients with inflammatory arthritis and 16 synovial fluid samples, including seven contemporaneous blood/synovial fluid pairs (online supplemental table 1).

To analyse global data structure, we extracted median expression values for each protein in each sample and calculated Spearman correlation coefficients between samples based on expression data. Hierarchical clustering revealed complete overlap in peripheral blood neutrophils between healthy donors and patients with inflammatory arthritis, indicating few systematic differences in global protein expression (figure 4A). Correspondingly, we found differential expression only of a single marker, CD64, between healthy and arthritic donor peripheral blood neutrophils after correction for multiple comparisons (figure 4C). These results mirror our transcriptomic findings and show similarity of blood neutrophils between healthy and arthritic donors.

By contrast, comparison of blood and synovial fluid revealed a strong separation driven by tissue (figure 4B). This separation was driven by multiple differentially expressed proteins in synovial fluid neutrophils, including downregulation of CXCR1 and upregulation of the integrin CD11c, PD-L1, ICAM-1, HLA-DR, the low-affinity Fc receptor CD32 (FcγRII) and CXCR4 (CD184), the receptor for CXCL12/SDF-1 that retains neutrophils in inflamed sites[27] (figure 4D,E). CD64 was also overexpressed but did not reach significance in comparison to arthritic blood due to already higher expression in blood neutrophils (figure 4E). Compared with healthy blood neutrophils, synovial fluid neutrophils also overexpressed CD64, the activation and lineage markers CD66b and CD15, the lipopolysaccharide (LPS) coreceptor CD14, and the integrin CD49d (figure 4E).

PD-L1, HLA-DR and CD64 are upregulated in neutrophils exposed to IFN-γ, consistent with our transcriptomic signature data.[28–34] The IL-8 receptor CXCR1 was downregulated, potentially reflecting agonist-mediated internalisation of this G protein-coupled receptor. No change was noted in granule proteins, including for primary (azurophilic) granules (including myeloperoxidase (MPO), proteinase 3 (PR3) and arginase 1), secondary granules (including LL-37/cathelicidin, CD177

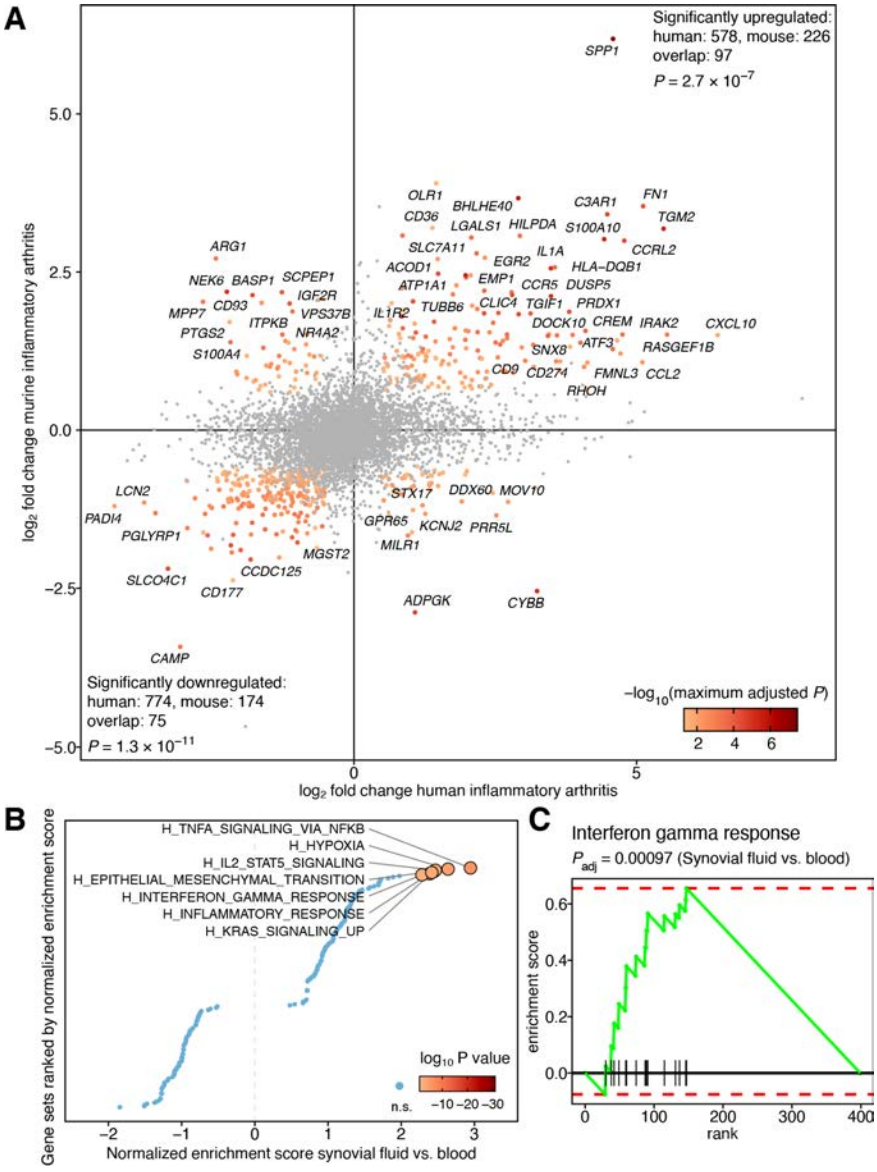

Figure 3 Cross-species analysis of neutrophil gene expression in inflamed synovial fluid. (A) Depicted is the $\log_2$ fold change of gene expression in human (x) versus murine (y) synovial fluid neutrophils compared with blood neutrophils. Only genes with one-to-one orthologues are shown and genes with adjusted p<0.05 in both comparisons and $|\log_2 \text{fold change}| \geq 0.75$ are highlighted. Genes are conservatively coloured by highest P value. (B) Significantly differentially expressed genes were ranked by $\log_2$ fold change, and gene set enrichment analysis was performed on 50 hallmark and 292 Biocarta gene sets. (C) Enrichment plot of the hallmark gene set 'interferon gamma response'. Only genes with one-to-one orthologues between mice and humans are shown; for gene symbols, the human symbol is shown.

and OLFM4) and tertiary granules (arginase 1). Results for all markers are shown in online supplemental figure 3.

We investigated how well expression differences in RNA and protein match each other. We found that downregulation of *CXCR1* and upregulation of *CXCR4*, *ICAM1*, *HLA-DRA*, *HLA-DRB1*, *HLA-DRB5* and *CD274* (encoding PD-L1) were highly concordant between RNA and protein (figure 4F). Upregulation of *FCGR1A* (CD64) and *FCGR2B* (CD32) was also observed on both RNA and protein level but was significant only at either gene (*FCGR1A*) or protein (CD32) level. This set of genes and their protein products thus constitute hallmarks of the synovial fluid neutrophil phenotype.

Continuous and discrete neutrophil phenotypes

To define neutrophil heterogeneity at the single-cell level, we performed uniform manifold approximation and projection (UMAP) dimensionality reduction on our CyTOF data. Initial results were dominated by the two known dichotomously expressed neutrophil proteins, CD177 and OLFM4 (online supplemental figure 4A). Cells from peripheral blood and synovial fluid were evenly distributed across $CD177^{pos/neg}$ and $OLFM4^{pos/neg}$ populations in the UMAP embedding, suggesting that the phenotypical changes distinguishing blood and synovial fluid neutrophils operate evenly across these markers (online supplemental figure 4B). Accordingly, we did not detect any significant differences in frequency of neutrophil subsets defined by CD177 or OLFM4 between blood and synovial fluid (online supplemental figure 4C).

To neutralise this dominant impact, we excluded CD177-anchored, OLFM4-anchored and the CD177-anchored enzyme PR3 from consideration and repeated dimensionality reduction. We observed a striking separation between resting blood

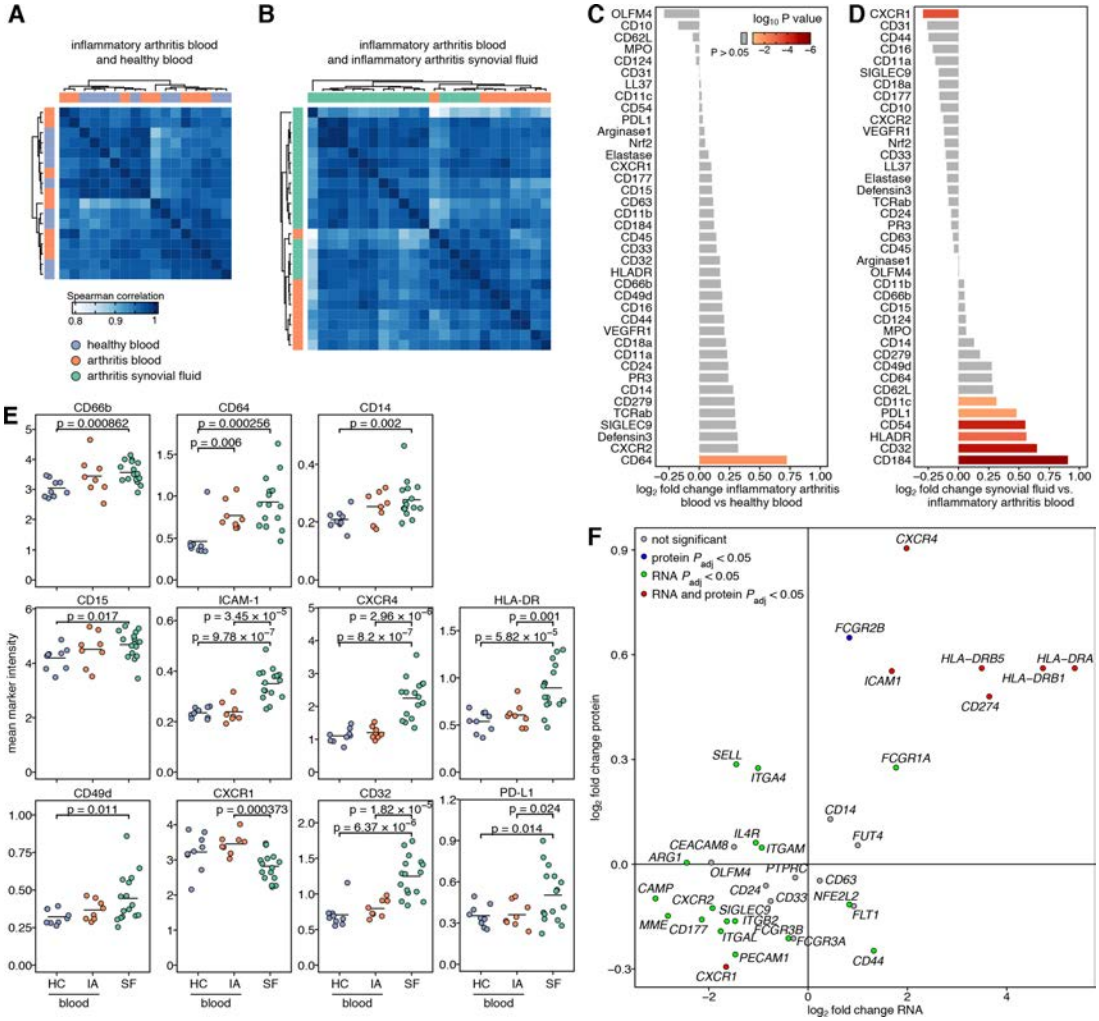

Figure 4 Mass cytometry analysis of neutrophils. (A) Hierarchical clustering of Spearman correlation coefficients between blood neutrophils from healthy donors and patients with inflammatory arthritis based on global neutrophil protein expression. (B) Differential expression analysis of global neutrophil marker expression in the peripheral blood. (C) Hierarchical clustering of Spearman correlation coefficients between peripheral blood and synovial fluid samples. (D) Differential expression analysis of global neutrophil marker expression between peripheral blood and synovial fluid. (E) Average expression of significantly differentially expressed markers per sample. (F) Comparison of gene and protein expression differences between blood and synovial fluid neutrophils identifies a hallmark synovial fluid phenotype. HC, healthy control; IA, inflammatory arthritis; SF, synovial fluid.

neutrophils and synovial fluid cells, single-cell findings that mirrored our bulk transcriptomic results (figure 5A). Synovial fluid neutrophils concentrated in two primary clusters, termed here SFN1 and SFN2 and observed across individual donors (figure 5A and online supplemental figure 5). For analysis purposes, we forced neutrophils into k=20 clusters, again excluding CD177, OLFM4 and PR3, with the goal of maximising the opportunity to identify distinct phenotypical states (figure 5B). Individual markers varied among the 20 clusters, confirming neutrophil heterogeneity at the single-cell level (figure 5C). Examining the frequency of cells belonging to each cluster, we observed considerable divergence among donors, limiting statistical power in this relatively small sample size. Clusters 10–12 were particularly over-represented in synovial fluid, representing the bulk of neutrophils in SFN2 (figure 5D). Neutrophils in clusters 10 and 11 expressed high levels of CXCR4 (CD184), and cluster 12 cells additionally expressed the IFN-γ markers HLA-DR, PD-L1 and CD64. The SFN1 population was contained within cluster 2 and was driven primarily by a single donor, although it trended higher across multiple samples in synovial fluid versus blood. By contrast, blood neutrophils were enriched for clusters 1, 8, 9 and 16, with only Cluster 9 (expressing high levels of granule proteins) and cluster 16 (expressing granule proteins, OLFM4 and CD124, the alpha chain of the IL-4 and IL-13 receptors) achieving statistical significance (figure 5D).

Expression of differentially expressed markers between blood and synovial fluid revealed that most markers follow expression gradients (figure 5E). Broadly, two gradients could be observed: a gradient from top to bottom that included many granule proteins and likely reflecting maturation (CD10, Nrf2, arginase 1, CD11a, elastase, LL-37, CD31, MPO, OLFM4, CD177 and CD184/CXCR4) and a gradient from left to right likely reflecting activation (CD66b, CD11b, CD15, CD16, CXCR1 and CD45) (online supplemental figure 5). Small populations of interest included clusters 8 and 19 expressing TCRαβ, equally rare in blood and synovial fluid, and cluster 6 expressing VEGFR1 and therefore potentially representing proangiogenic neutrophils,[35] significantly increased in synovial fluid compared with healthy blood.

Notably, not all upregulated markers were expressed on the same cells. For example, CXCR4-high neutrophils expressed

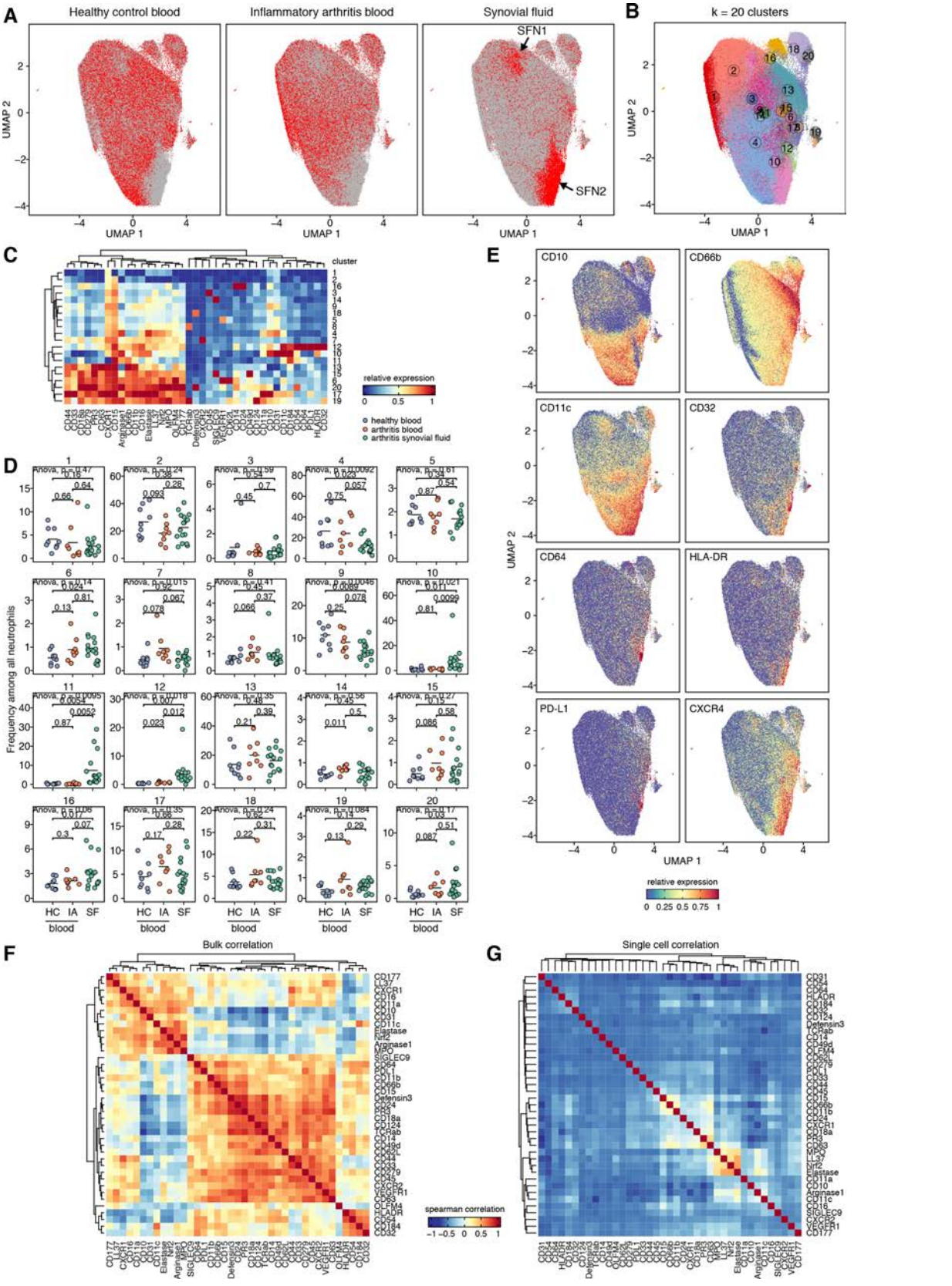

Figure 5 Continuous and discrete neutrophil phenotypes. (A) UMAP embedding of single-cell CyTOF data separates blood neutrophils and synovial fluid cells. (B) Overclustering of neutrophils into 20 groups captures neutrophil heterogeneity across blood and synovial fluid. (C) Heterogeneity in marker expression between the 20 clusters. (D) Change in frequency of different neutrophil phenotypes across conditions. (E) Gradients of marker expression characterise synovial fluid neutrophils. Correlation between markers on a per-sample (F) and single-cell (G) level identifies clusters of coexpressed markers. ANOVA, analysis of variance; CyTOF, cytometry by time of flight; HC, healthy control; IA, inflammatory arthritis; SF, synovial fluid; UMAP, uniform manifold approximation and projection.

variable amounts of HLA-DR and PD-L1 (figure 5E). Correlating expression intensity on a per-sample bulk level revealed a positive correlation between markers defining the core synovial fluid phenotype: HLA-DR, ICAM-1, CXCR4 and CD32 (figure 5F). Analysis at the single-cell level confirmed a correlation between general activation markers CD11b, CD15 and CD66b and within a cluster of granule proteins (MPO, LL-37, Nrf2 and elastase) but not between CXCR4, HLA-DR and PD-L1 (figure 5G).

Together, these results show that CXCR4+, HLA-DR+ and PD-L1+ neutrophils are expanded in inflamed synovial fluid and that expression of these markers peaks in different cells, confirming that the inflamed environment features divergent neutrophil phenotypes.

IFN-γ and ageing drive blood neutrophils toward a synovial fluid phenotype

Since both transcriptomic and proteomic analysis revealed a strong IFN-γ response signature in synovial fluid neutrophils, we hypothesised that stimulation with IFN-γ could recapitulate the synovial fluid phenotype in healthy blood neutrophils. As expected, viability dropped from nearly 100% at beginning of culture to 71% after 2 days of culture at 37°C. When IFN-γ was added at the beginning of culture, neutrophil survival increased to 87% (figure 6A).

IFN-γ stimulation prevented downregulation of CD32 and significantly upregulated CD64, ICAM-1, HLA-DR and PD-L1 (figure 6B). CXCR4 expression was not detectable in freshly isolated neutrophils but increased with time in culture, consistent with its known role as a marker of neutrophil ageing.[21] Interestingly, CXCR4 expression was reduced by cytokine stimulation, indicating either an impact on CXCR4 expression specifically or a broader effect on the neutrophil ageing programme (figure 6B).

Based on those findings, we hypothesised that cytokine stimulation and ageing were complementary in establishing the synovial fluid neutrophil phenotype. We therefore analysed unstimulated and stimulated neutrophils together in a single diffusion map. This analysis revealed a marked divergence in phenotypes between cells left unstimulated and those incubated with IFN-γ (figure 6C). CXCR4 expression was highest at the most distant pole of the unstimulated trajectory (figure 6D). Conversely, IFN-γ robustly upregulated HLA-DR, PD-L1 and ICAM-1 (figure 6D). Thus, the combination of ageing and exposure to IFN-γ, but not either alone, yielded a neutrophil phenotype resembling that of synovial fluid neutrophils.

DISCUSSION

Synovial fluid neutrophils are the hallmark of inflammatory arthritis.[36] We employed low-input RNAseq and CyTOF to characterise neutrophils from healthy donor blood and from blood and synovial fluid of patients with active arthritis. Whereas circulating neutrophils exhibited few changes with disease state, synovial fluid neutrophils displayed consistent phenotypical deviation implicating two conceptually orthogonal influences: response to local mediators, most prominently IFN-γ, and cell ageing.

The marked alteration in mRNA expressed by synovial fluid neutrophils is consistent with the growing understanding of neutrophils as highly dynamic cells that remain transcriptionally active throughout their life span.[19 37 38] This adaptability may be of particular consequence in neutrophils recruited to inflamed sites such as the arthritic joint, since cytokines can prolong neutrophil half-life from a baseline of 8–20 hours to several days.[39]

Transcriptional signatures observed here included response to mediators of established importance in arthritis, including tumour necrosis factor and IL-6, as well as to hypoxia, a known feature of the synovial environment.[40] The role of IFN-γ in arthritis is less well understood. Prior studies have identified elevated levels of IFN-γ in arthritic synovial fluid and, generally to a lesser extent, in arthritic blood.[41–46] Studies performed more than 20 years ago implicated IFN-γ in the induction of CD64 expression on synovial fluid neutrophils.[6] Potential IFN-γ sources suggested by human and/or murine arthritis studies include CD4 T cells (IFN-γ is the hallmark Th1 cytokine), CD8 T cells, NK cells and NKT cells.[47–52] Experimental overexpression of IFN-γ in the joint accelerates cartilage injury through upregulation of IgG Fc receptors and therefore enhanced susceptibility to immune complex injury.[53] However, IFN-γ-deficient mice exhibit normal susceptibility to IgG-mediated K/BxN serum transfer arthritis, while IFN-γ blockade or IFN-γ receptor deficiency accelerates the onset and severity of collagen-induced arthritis.[50 54 55] Trials of recombinant IFN-γ in rheumatoid arthritis found at best modest disease amelioration.[56 57] These findings reflect the net impact of IFN-γ on multiple lineages and remain compatible with the possibility that neutrophil exposure to IFN-γ in arthritis is proinflammatory (eg, through upregulation of surface Fc receptors and HLA-DR), anti-inflammatory (eg, through upregulation of the T cell inhibitor PD-L1) or both.

Comparing the transcriptional signature of human and murine neutrophils, we observed substantial overlap, including shared presence of an IFN-γ signature in synovial fluid neutrophils, supporting the human relevance of extensive murine work defining the role of neutrophils in arthritis.[11 13–16] This conclusion is important because unambiguous human studies are complicated by the lack of neutrophil-specific therapeutics. Cross-species similarity is further echoed in murine neutrophil scRNAseq data, where differences between healthy and arthritic blood neutrophils are small, whereas differences between arthritic blood and synovial neutrophils are large.[19] Whereas the neutrotime signature cannot be extrapolated directly to bulk RNAseq data, downregulation of early-neutrotime transcripts such as *LCN2*, *CAMP* and *CD177* further supports the suggestion that human synovial fluid neutrophils—like their murine counterparts—skew toward an aged phenotype reflecting prolonged survival in the inflamed joint.[19]

Of particular interest is the marked cell-to-cell heterogeneity revealed by CyTOF. The clusters reported here reflect investigator-chosen markers and analytical parameters, and therefore are best regarded as one snapshot of this complex population rather than as discrete subsets. The data show that neutrophils within the inflamed joint differ phenotypically from each other as well as from those in blood. Dimensionality reduction by UMAP identified two broad populations: SFN1, resembling circulating neutrophils, and SFN2, a more abundant group typically bearing markers associated with the IFN-γ signature. We speculate that these populations reflect a chronological progression, with SFN1 representing recent arrivals that evolve into SFN2 cells with exposure to the inflamed synovial environment and with time. This suggestion is consistent with greater SFN2 expression of the maturity marker CD10 and the ageing marker CXCR4, although these neutrophils remain internally diverse.[58]

We applied both inflammatory stimuli and time to cultured healthy donor blood neutrophils. Two orthogonal signals were noted: IFN-γ exposure upregulated hallmark SFN2 proteins

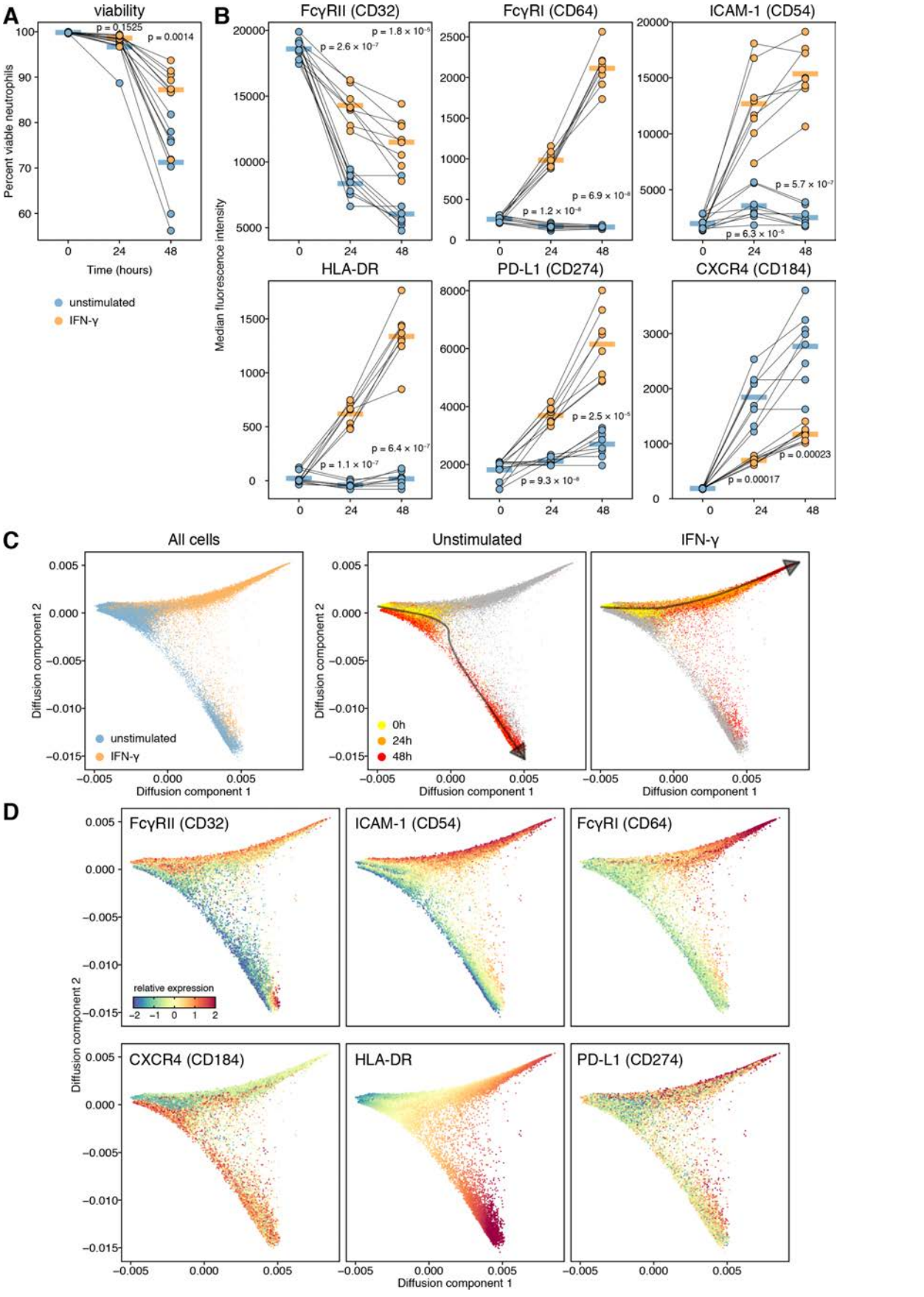

Figure 6 Progressive ageing and response to IFN-γ recapitulate the synovial fluid phenotype in vitro. (A) Stimulation with IFN-γ extends the lifetime of neutrophils in vitro. (B) Effect of ageing and IFN-γ on the expression of key surface markers. (C) Diffusion map of unstimulated and IFN-γ-stimulated neutrophils cultured over 48 hours. (D) Expression of key surface markers on the diffusion map. IFN-γ, interferon gamma.

such as HLA-DR, PD-L1 and CD64, while ageing was required to yield the second key SFN2 marker, CXCR4 (interestingly partially suppressed by IFN-γ). Further study will be required to confirm the parallels between these findings and the arthritis context, but the data support the conceptual model that the neutrophil phenotypes observed in human synovial fluid represent an integration of inflammatory stimuli and ageing in cells recruited in an ongoing manner to the inflamed joint.

Our work has several limitations. RNAseq studies employed bulk sorted neutrophils, enabling us to identify transcripts in depth but prohibiting us from calculating developmental trajectories. Future studies using scRNAseq will be required to define the ontological relationships among joint fluid neutrophils. In our CyTOF studies, not all antigens proved interpretable for technical reasons, and it is likely that some informative antigens were omitted. Our data do not detail epigenetic reprogramming of neutrophils, and we did not characterise the function of the heterogeneous groups identified in arthritic synovial fluid. Despite these limitations, the results represent a uniquely granular examination of the transcriptional and surface/intracellular phenotype of human arthritic neutrophils, setting the stage for the next set of phenotypical and functional studies toward the ultimate goal of identifying targetable pathways for therapeutic neutrophil blockade in arthritis.

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Contributors RG-B conceptualised the study; acquired patient samples and healthy donor samples; performed neutrophil isolation, cell sorting, RNA extraction, cryopreservation of fresh neutrophils; designed the mass cytometry panel; performed and guided RNA sequencing (RNAseq) and mass cytometry data analysis; designed the neutrophil ex vivo culture system; guided the validation experiments; created the figures; and wrote the manuscript. TE performed in vitro validation experiments on prospectively collected healthy donor neutrophils and analysed mass cytometry data. NSH performed RNAseq data analysis and improved visualisation techniques. FAR performed RNAseq data analysis. SAJ performed RNAseq and mass cytometry data analysis. OH acquired patient samples and healthy donor samples; performed neutrophil isolation, cell sorting, cryopreservation of fresh neutrophils and designed the mass cytometry panel. AW performed neutrophil isolation, cell sorting and cryopreservation of fresh neutrophils. EK analysed the data. JB and JS performed RNAseq and mass cytometry data analysis. HJ, LAH and DAR acquired patient samples. CM-T and H-ML analysed data. GW designed the neutrophil ex vivo culture system, provided critical input for validation experiments and analysed the data. JAL performed mass cytometry analysis. AH performed and guided RNAseq and mass cytometry data analysis. PAN conceptualised the study, acquired patient samples and healthy donor samples, designed the mass cytometry panel, guided data analysis, guided the validation experiments and wrote the manuscript. Guarantors: RG-B, PAN.

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Patient consent for publication Not applicable.

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Data availability statement Data are available in a public, open access repository. All data relevant to the study are included in the article. All relevant data are included in the article and online supplemental information. RNA-sequencing data were deposited in GEO (accession number GSE193117).[59] Cytometry by time of flight data were deposited in flow repository (accession number FR-FCM-Z4TF).[60]

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CLINICAL SCIENCE

Efficacy and safety of selective TYK2 inhibitor, deucravacitinib, in a phase II trial in psoriatic arthritis

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ABSTRACT

Objective To evaluate the efficacy and safety of an oral selective tyrosine kinase 2 (TYK2) inhibitor, deucravacitinib, in patients with active psoriatic arthritis (PsA).

Methods In this double-blind, phase II trial, 203 patients with PsA were randomised 1:1:1 to placebo, deucravacitinib 6 mg once a day or 12 mg once a day. The primary endpoint was American College of Rheumatology-20 (ACR-20) response at week 16.

Results ACR-20 response was significantly higher with deucravacitinib 6 mg once a day (52.9%, p=0.0134) and 12 mg once a day (62.7%, p=0.0004) versus placebo (31.8%) at week 16. Both deucravacitinib doses resulted in significant improvements versus placebo (p≤0.05) in the multiplicity-controlled secondary endpoints of change from baseline in Health Assessment Questionnaire-Disability Index and Short Form-36 Physical Component Summary score and in Psoriasis Area and Severity Index-75 response. Improvements were also seen in multiple exploratory endpoints with deucravacitinib treatment. The most common adverse events (AEs) (≥5%) in deucravacitinib-treated patients were nasopharyngitis, upper respiratory tract infection, sinusitis, bronchitis, rash, headache and diarrhoea. There were no serious AEs and no occurrence of herpes zoster, opportunistic infections and major adverse cardiovascular events, or differences versus placebo in mean changes in laboratory parameters with deucravacitinib treatment.

Conclusions Treatment with the selective TYK2 inhibitor deucravacitinib was well tolerated and resulted in greater improvements than placebo in ACR-20, multiplicity-controlled secondary endpoints and other exploratory efficacy measures in patients with PsA. Larger trials over longer periods of time with deucravacitinib are warranted to confirm its safety profile and benefits in PsA.

Trial registration number NCT03881059.

Key messages

What is already known about this subject?

⇒ Interleukin 23 is a key cytokine in the pathogenesis of psoriatic arthritis, psoriasis and other immune-mediated diseases, and its signalling is mediated by the intracellular kinase, tyrosine kinase 2 (TYK2).

⇒ Deucravacitinib is a novel oral selective TYK2 inhibitor that binds to the unique regulatory domain of TYK2 with high selectivity, in contrast to inhibitors of closely related Janus kinases 1/2/3 that bind the conserved active domain.

What does this study add?

⇒ Deucravacitinib at 6 mg and 12 mg doses once a day demonstrated greater efficacy versus placebo at week 16, with improvements observed across all American College of Rheumatology domains, enthesitis endpoints, and multiple patient-reported, psoriasis-related and composite outcomes in patients with active psoriatic arthritis.

⇒ Treatment with deucravacitinib was generally well tolerated, and the safety and laboratory parameter profile of deucravacitinib was consistent with its selective mechanism of action and with that observed in an earlier phase II psoriasis trial and recently reported phase III trials in psoriasis.

How might this impact on clinical practice or future developments?

⇒ The options for targeted oral therapies in psoriatic arthritis are limited; deucravacitinib, which demonstrated improved efficacy versus placebo and was well tolerated, may be a promising option for treatment of patients with active psoriatic arthritis.

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INTRODUCTION

Psoriatic arthritis (PsA) is a heterogeneous disease with diverse manifestations, including arthritis, enthesitis, dactylitis, and skin and nail lesions.[1 2] Up to 30% of patients with psoriasis (PsO) can develop PsA.[1 2] Patients with PsA are at an increased risk of developing serious comorbidities,[2 3] which can increase the risk of death.[4] A substantial proportion of patients with PsA are inadequately treated with currently available therapeutic options; many of these medications have safety concerns and have inconvenient dosing, and few patients reach treatment targets, such as achievement of minimal disease activity (MDA). This results in disease progression and disability, frequent medication switching, and higher overall treatment costs.[5 6] Therapies with new modes of action that are safe, effective and have convenient dosing are needed to control the spectrum of disease manifestations and

improve the quality of life of patients with PsA as another option for treatment, including in those who do not respond to other modalities.[7 8]

Tyrosine kinase 2 (TYK2) is an intracellular kinase that is a member of the Janus kinase (JAK) family of kinases which signal through the JAK–signal transducer and activator of transcription pathway. TYK2 mediates signalling by cytokines such as interleukin (IL) 23 that are involved in the pathogenesis of PsO, PsA and other immune-mediated diseases.[9 10] TYK2 signalling pathways are restricted to select immune pathways unlike those of the other members of the JAK family, JAK 1/2/3, which are involved in broader immune (eg, T cells and natural killer cells) as well as in extraimmune pathways (eg, bone marrow effects, lipid metabolism).[11] IL-23 is involved in the activation and proliferation of Th17 cells linked to sustained inflammatory responses in the skin and joints in PsA, and anti-IL-23 antibodies have shown efficacy in PsO and PsA.[2 12] Patients with early PsA who do not achieve MDA with standard methotrexate therapy have higher levels of IL-23 than those who respond to methotrexate.[13]

Deucravacitinib is a novel oral selective TYK2 inhibitor with a unique mechanism of action distinct from that of inhibitors of JAK 1/2/3.[9] Deucravacitinib binds to the regulatory or pseudokinase domain of TYK2 and inhibits the enzyme via a conformational change that locks the enzyme in an inactive state. This is in contrast to inhibitors of JAK 1/2/3 and other kinases that act on the conserved active domains at the adenosine 5′-triphosphate binding site. This allosteric inhibition results in 100-fold to 2000-fold selectivity for TYK2 over JAK 1/2/3 in in vitro cellular assays.[9]

Deucravacitinib was shown to be efficacious in phase II and phase III trials in PsO and was well tolerated overall with generally mild to moderate adverse events (AEs).[14 15] No opportunistic infections or laboratory abnormalities characteristic of JAK 1/2/3 inhibitors were observed with deucravacitinib treatment.[14–18]

This phase II trial evaluated the efficacy and safety of deucravacitinib in patients with active PsA at two doses. Deucravacitinib was administered at randomisation at a dosage of 6 mg once a day, the dosage that was selected for phase III trials in PsO based on the phase II results, as well as at a dosage of 12 mg once a day to evaluate whether higher exposures could lead to better efficacy in joints, as has been seen with some other agents.[14 15 19 20]

METHODS

Trial design

This randomised, multicentre, double-blind, phase II trial was conducted in the Czech Republic, Germany, Hungary, Poland, Spain, Russia and USA. The results from the initial 16-week placebo-controlled period (part A) of the trial (see study design in online supplemental figure S1) are presented in this article. Eligible patients had a diagnosis of PsA for ≥6 months and fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR) at screening, had active joint disease (at least three tender and at least three swollen joints), a high-sensitivity C reactive protein (hs-CRP) level of ≥3 mg/L (upper limit of normal, 5 mg/L) and ≥1 plaque PsO lesion (≥2 cm).[21] They had to have failed to respond or were intolerant to ≥1 prior therapy, which could include non-steroidal anti-inflammatory drugs, corticosteroids, conventional synthetic disease-modifying antirheumatic drugs (csDMARD) and/or one tumour necrosis factor inhibitor (TNFi). Concomitant use of a csDMARD (eg, methotrexate, leflunomide, sulfasalazine or hydroxychloroquine) was permitted if used for ≥3 months with a stable dose for ≥28 days prior to the trial. Additional eligibility criteria are listed in the online supplemental materials.

Eligible patients were randomised 1:1:1 to oral placebo once a day, deucravacitinib 6 mg once a day or deucravacitinib 12 mg once a day for 16 weeks. Randomisation was stratified according to previous TNFi use (experienced/naïve) and body weight (≥90 kg and <90 kg). A randomisation list was generated by an interactive response technology using a permuted block design within each combination of stratum level. Investigative site staff, study sponsor and patients remained blinded to treatment assignment. Patients provided written informed consent before trial entry.

Endpoints

The primary endpoint was American College of Rheumatology-20 (ACR-20) response at week 16, defined as meeting the following criteria: ≥20% improvement from baseline in the number of tender joints (68 total joint count); ≥20% improvement from baseline in the number of swollen joints (66 total joint count); and ≥20% improvement from baseline in at least three of the following five domains: patient global assessment of pain, patient global assessment of disease activity, physician global assessment of disease activity, Health Assessment Questionnaire-Disability Index (HAQ-DI) and hs-CRP. Multiplicity-controlled secondary efficacy endpoints were evaluated using hierarchical testing at week 16 and included (1) improvement from baseline in physical function as measured by HAQ-DI; (2) improvement in psoriatic skin lesions as measured by Psoriasis Area and Severity Index (PASI) 75 response (≥75% reduction from baseline in PASI scores) in patients with ≥3% body surface area involvement at baseline; and (3) change from baseline in the quality of life measure, Short Form-36 (SF-36) Physical Component Summary (PCS) score. Additional endpoints evaluated at week 16 which were not multiplicity-controlled included the proportion of patients achieving higher ACR thresholds of efficacy (ACR-50 and ACR-70 responses); HAQ-DI response (≥0.35 improvement from baseline (minimum clinically important difference in PsA)); resolution of enthesitis (Leeds Enthesitis Index (LEI) of 0 in patients with LEI ≥1 at baseline); resolution of dactylitis (score of 0 in patients with ≥1 tender and swollen digit at baseline); mean changes from baseline in Psoriatic Arthritis Disease Activity Score (PASDAS), Disease Activity Index for Psoriatic Arthritis (DAPSA) and SF-36 Mental Component Summary (MCS) score; and achievement of MDA (defined as achieving at least five of the following: tender joint count ≤1; swollen joint count ≤1; PASI ≤1 or body surface area ≤3%; tender enthesal points ≤1; patient global assessment of pain ≤15; patient global assessment of disease activity ≤20; and HAQ-DI ≤0.5). A full listing of all endpoints is provided in the online supplemental materials. Comparisons between treatment groups over time were also evaluated as exploratory endpoints. Safety assessments, including reporting of AEs, physical examinations, vital signs, ECG and laboratory parameters were conducted periodically throughout the trial.

Statistical analysis

Sample size and power determination are described in the online supplemental materials. The primary efficacy analysis used a logistic regression model to assess whether there was a dose–response trend between ACR-20 response and dose level at week 16. This model included dose level as a continuous variable, and TNFi use (experienced/naïve) and body weight (≥90 kg/<90 kg) as covariates. The OR versus placebo and the corresponding two-sided 95% CI were estimated by

Cochran-Mantel-Haenszel test with stratification factors (body weight and TNFi use). Patients who discontinued the trial early, started a prohibited treatment, were lost to follow-up or had no ACR-20 assessments at week 16 had outcomes imputed as non-responses in an intention-to-treat analysis. A Cochran-Mantel-Haenszel test was applied to assess the robustness of the results for the primary endpoint by predefined subgroups based on stratification factors.

Statistical analysis of secondary endpoints at week 16 was performed in the following hierarchical order to control for multiplicity: (1) change from baseline in HAQ-DI score, (2) PASI-75 response and (3) change from baseline in SF-36 PCS. Secondary endpoint analyses are further described in the online supplemental materials. Any reported p values in the tests for additional endpoints will be considered nominal.

Patient and public involvement

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

RESULTS

Patients

The trial was initiated on 28 March 2019, with the last patient's last visit of the 16-week placebo-controlled period occurring on 27 April 2020. Of 314 patients screened, 203 were randomised and received treatment (placebo, n=66; deucravacitinib 6 mg once a day, n=70; deucravacitinib 12 mg once a day, n=67). Of the randomised patients, 180 (89%) completed 16 weeks of treatment, with the most common causes of discontinuation being AEs and patient withdrawal across the treatment arms (online supplemental figure S2).

Demographic and baseline disease characteristics were overall similar across the three treatment groups. The mean age was 49.8 years, 51.2% were female, 98% were Caucasians, the mean body weight was 88.6 kg, 65.0% were being treated with csDMARDs at baseline and 15.8% had previously been treated with a TNFi (table 1). In addition, the median PsA duration (from diagnosis) was 4.5 years, the mean swollen joint count was 11.3, the mean tender joint count was 18.1, enthesitis (LEI) was present in 47.3%, dactylitis in 38.9%, and the mean PASI

Table 1 Baseline demographic and clinical characteristics

	Total N=203	Placebo n=66	Deucravacitinib 6 mg once a day n=70	Deucravacitinib 12 mg once a day n=67
Demographics				
Age, years, mean (SD)	49.8 (13.5)	48.5 (13.2)	50.5 (13.7)	50.5 (13.8)
Female, n (%)	104 (51.2)	40 (60.6)	30 (42.9)	34 (50.7)
White, n (%)	199 (98.0)	65 (98.5)	67 (95.7)	67 (100.0)
Body weight, kg, mean (SD)	88.6 (19.0)	90.5 (22.7)	86.4 (16.6)	89.1 (17.3)
<90 kg, n (%)	104 (51.2)	33 (50.0)	36 (51.4)	35 (52.2)
≥90 kg, n (%)	99 (48.8)	33 (50.0)	34 (48.6)	32 (47.8)
BMI, kg/m^2, mean (SD)	30.4 (6.0)	31.2 (7.2)	29.6 (5.4)	30.3 (5.4)
Prior/concomitant medications				
Use of csDMARD, n (%)	132 (65.0)	44 (66.7)	45 (64.3)	43 (64.2)
Use of methotrexate, n (%)	111 (54.7)	39 (59.1)	35 (50.0)	37 (55.2)
Weekly dose, mg, mean (SD)	16.5 (4.7)	16.7 (4.8)	16.4 (4.9)	16.5 (4.6)
Prior TNFi use, n (%)				
1	31 (15.3)	11 (16.7)	12 (17.1)	8 (11.9)
2	1 (0.5)	0	0	1 (1.5)
Oral steroid use, n (%)	25 (12.3)	12 (18.2)	7 (10.0)	6 (9.0)
Daily dose, mg, mean (SD)	4.0 (1.7)	4.4 (1.9)	3.7 (1.3)	3.5 (1.6)
Disease parameters				
Psoriatic arthritis disease duration from diagnosis, years, median (range)	4.5 (0.1–42.8)	4.5 (0.6–22.9)	5.3 (0.1–42.8)	3.8 (0.6–27.7)
Tender joint count, mean (SD)	18.1 (10.7)	16.9 (9.8)	18.1 (10.3)	19.4 (11.8)
Swollen joint count, mean (SD)	11.3 (7.9)	10.5 (7.7)	11.9 (7.0)	11.3 (9.0)
Pain in mm, VAS, mean (SD)*	64.1 (18.7)	64.9 (18.2)	63.6 (21.7)	63.8 (15.9)
HAQ-DI, mean (SD)	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)
hs-CRP, mg/L, mean (SD)	18.2 (29.0)	20.4 (39.1)	17.6 (23.6)	16.5 (21.7)
Psoriasis with ≥3% BSA, n (%)	165 (81.3)	54 (81.8)	59 (84.3)	52 (77.6)
PASI-75 score in patients with ≥3% BSA				
Mean (SD)	8.5 (6.7)	9.1 (7.4)	8.5 (6.8)	7.9 (5.9)
Range	1.2–33.8	1.2–31.4	1.6–33.8	1.4–31.8
Enthesitis, Leeds Index ≥1, n (%)	96 (47.3)	31 (47.0)	39 (55.7)	26 (38.8)
Leeds Index in those with enthesitis, mean (SD)	2.7 (1.6)	2.8 (1.7)	2.5 (1.6)	2.9 (1.4)
Dactylitis, n (%)	79 (38.9)	25 (37.9)	30 (42.6)	24 (35.8)

*VAS scale ranges from 0–100 mm, with higher values indicating worse pain.
BMI, body mass index; BSA, body surface area; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire-Disability Index; hs-CRP, high-sensitivity C reactive protein; PASI-75, 75% improvement from baseline in Psoriasis Area and Severity Index; TNFi, tumour necrosis factor inhibitor; VAS, Visual Analogue Scale.

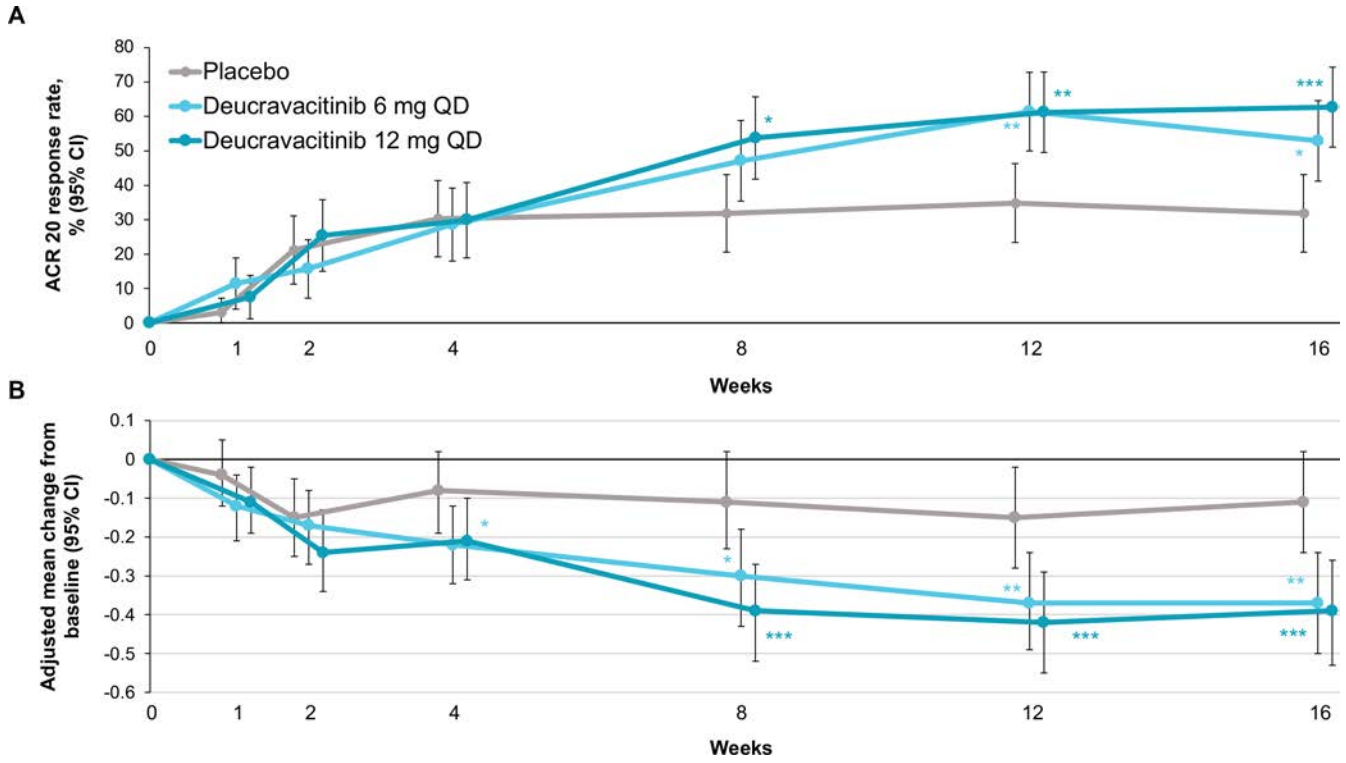

Figure 1 ACR-20 response and change in HAQ-DI score over time. Supporting values are shown in online supplemental table S4. (A) Time course of ACR-20 response through week 16. Response rates are reported in the intention-to-treat population (ie, all randomised patients) with non-responder imputation; patients who discontinued the trial early, started a prohibited treatment, were lost to follow-up or had no ACR assessments had outcomes imputed as non-responses. (B) Adjusted mean change from baseline in HAQ-DI score through week 16. Placebo, n=66; deucravacitinib 6 mg once a day, n=70; deucravacitinib 12 mg once a day, n=67. P values indicate a difference from placebo: *p<0.05, **p≤0.01, ***p≤0.001, adjusted for multiplicity at week 16 only. ACR, American College of Rheumatology; HAQ-DI, Health Assessment Questionnaire-Disability Index; QD, once a day.

score was 8.5 in those with body surface area of involvement ≥3%.

Efficacy

The study met its primary objective, with ACR-20 response being significantly higher with deucravacitinib 6 mg once a day (52.9%) and 12 mg once a day (62.7%) versus placebo (31.8%) at week 16. The adjusted OR (95% CI) for deucravacitinib 6 mg once a day versus placebo was 2.4 (1.2 to 4.8) (p=0.0134) and for deucravacitinib 12 mg once a day versus placebo was 3.6 (1.8 to 7.4) (p=0.0004). Numerical improvements in ACR-20 response were observed from week 8 onwards at both deucravacitinib doses versus placebo (figure 1A). Higher ACR-20 response was seen with deucravacitinib treatment versus placebo regardless of prior TNFi exposure (experienced vs naïve), body weight (<90 kg vs ≥90 kg) or gender (male vs female) (online supplemental figure S3). Mean improvements in individual ACR components from baseline were greater with each deucravacitinib dose versus placebo (online supplemental table S1).

Other efficacy endpoints at week 16 were also numerically higher with both deucravacitinib doses compared with placebo, including ACR-50, ACR-70 and HAQ-DI responses (nominal p≤0.05; table 2). The mean improvements from baseline in HAQ-DI scores at week 16 were significantly higher with deucravacitinib 6 mg and 12 mg once a day versus placebo (p≤0.002), with improvements evident as early as week 4 with both deucravacitinib doses (figure 1B). Higher PASI-75 response was observed in patients with PsO involving ≥3% body surface area at baseline with deucravacitinib 6 mg once a day (42.4%; adjusted OR 2.9 (95% CI 1.3 to 6.7); p=0.0136) and 12 mg once a day (59.6%; OR 5.8 (95% CI 2.4 to 13.8); p<0.0001) versus placebo (20.4%) at week 16. Significantly greater improvements from baseline were seen at week 16 with deucravacitinib treatment at both doses versus placebo in SF-36 PCS, as well as numerical improvements in SF-36 MCS scores (p≤0.0062 and nominal p≤0.0263, respectively; table 2). Higher numbers of patients treated with deucravacitinib 6 mg once a day and 12 mg once a day versus placebo achieved enthesitis resolution (51.3%, 50.0%, 22.6%), dactylitis resolution (76.7%, 79.2%, 60.0%) and MDA (22.9%, 23.9%, 7.6%), and showed greater mean change from baseline in PASDAS (−2.0, –2.1, −1.1) and DAPSA scores (−23.2, –25.6, −13.3), respectively (table 2).

Safety

AEs were observed at a higher frequency at both deucravacitinib doses (65.7%) compared with placebo (42.4%) (table 3). The most common AEs (≥5%) in deucravacitinib-treated patients were nasopharyngitis, upper respiratory tract infection, sinusitis, bronchitis, rash, diarrhoea and headache (table 3), with most AEs being of mild to moderate severity. Acne was reported in 2 of 70 (2.9%) patients in the 6 mg once a day deucravacitinib treatment group, 1 of 67 (1.5%) in the 12 mg once a day group, and 0 of 66 (0.0%) in the placebo group; dermatitis acneiform was reported in 2 of 70 (2.9%), 2 of 67 (3.0%) and 0 of 66 (0.0%), respectively. No serious AEs (including serious infections) were reported in deucravacitinib-treated patients. There were no thrombotic events in the deucravacitinib groups; one patient in the placebo group with a family history of thrombophilia had a serious AE of deep vein thrombosis. There was no occurrence of herpes zoster, tuberculosis, opportunistic infection

Table 2 Efficacy endpoints at week 16

Endpoint	Placebo n=66	Deucravacitinib 6 mg once a day n=70	Deucravacitinib 12 mg once a day n=67
Primary endpoint			
ACR-20			
Response rate, % (95% CI)	31.8 (20.6 to 43.1)	52.9 (41.2 to 64.6)	62.7 (51.1 to 74.3)
Adjusted OR vs placebo (95% CI)		2.4 (1.2 to 4.8)	3.6 (1.8 to 7.4)
P value		0.0134*	0.0004*
Secondary endpoints			
HAQ-DI			
Adjusted mean change from baseline (95% CI)	−0.1 (−0.2 to 0.0)	−0.4 (−0.5 to −0.2)	−0.4 (−0.5 to −0.3)
Difference from placebo (95% CI)		−0.3 (−0.4 to −0.1)	−0.3 (−0.5 to −0.1)
P value		0.0020*	0.0008*
PASI-75			
Response rate, % (95% CI)	20.4 (9.6 to 31.1)	42.4 (29.8 to 55.0)	59.6 (46.3 to 73.0)
Adjusted OR vs placebo (95% CI)		2.9 (1.3 to 6.7)	5.8 (2.4 to 13.8)
P value		0.0136*	<0.0001*
SF-36 PCS			
Adjusted mean change from baseline (95% CI)	2.3 (0.4 to 4.2)	5.6 (3.8 to 7.5)	5.8 (3.9 to 7.7)
Difference from placebo (95% CI)		3.3 (0.9 to 5.7)	3.5 (1.1 to 5.9)
P value		0.0062*	0.0042*
Additional endpoints			
ACR-50			
Response rate, % (95% CI)	10.6 (3.2 to 18.0)	24.3 (14.2 to 34.3)	32.8 (21.6 to 44.1)
Adjusted OR vs placebo (95% CI)		2.7 (1.1 to 7.1)	4.2 (1.7 to 10.9)
P value		0.0326	0.0016
ACR-70			
Response rate, % (95% CI)	1.5 (0.0 to 4.5)	14.3 (6.1 to 22.5)	19.4 (9.9 to 28.9)
Adjusted OR vs placebo (95% CI)		12.0 (1.5 to 99.3)	19.0 (2.3 to 155.2)
P value		0.0044	0.0003
HAQ-DI			
Response rate†, % (95% CI)	15.2 (6.5 to 23.8)	38.6 (27.2 to 50.0)	40.3 (28.6 to 52.0)
Adjusted OR vs placebo (95% CI)		3.8 (1.6 to 8.8)	3.7 (1.6 to 8.4)
P value		0.0019	0.0015
SF-36 MCS			
Adjusted mean change from baseline (95% CI)	0.7 (−1.3 to 2.7)	3.6 (1.7 to 5.5)	3.5 (1.5 to 5.5)
Adjusted mean difference from placebo (95% CI)		2.9 (0.4 to 5.3)	2.8 (0.3 to 5.3)
P value		0.0211	0.0263
Enthesitis resolution (LEI)	n=31	n=39	n=26
Response rate, % (95% CI)	22.6 (7.9 to 37.3)	51.3 (35.6 to 67.0)	50.0 (30.8 to 69.2)
Adjusted OR vs placebo (95% CI)		3.6 (1.3 to 10.3)	3.4 (1.1 to 10.7)
P value		0.0138	0.0393
Dactylitis resolution	n=25	n=30	n=24
Response rate, % (95% CI)	60.0 (40.8 to 79.2)	76.7 (61.5 to 91.8)	79.2 (62.9 to 95.4)
Adjusted OR vs placebo (95% CI)		2.2 (0.7 to 7.1)	2.8 (0.8 to 10.5)
P value		NA	NA
PASDAS			
Adjusted mean change from baseline (95% CI)	−1.1 (−1.5 to −0.7)	−2.0 (−2.4 to −1.6)	−2.1 (−2.5 to −1.8)
Adjusted mean difference from placebo (95% CI)		−0.9 (−1.4 to −0.4)	−1.1 (−1.5 to −0.6)
P value		0.0003	<0.0001
DAPSA			
Adjusted mean change from baseline (95% CI)	−13.3 (−17.7 to −9.0)	−23.2 (−27.5 to −19.0)	−25.6 (−30.0 to −21.2)
Adjusted mean difference from placebo (95% CI)		−9.9 (−15.3 to −4.5)	−12.3 (−17.7 to −6.8)
P value		0.0004	<0.0001
MDA			
Response rate, % (95% CI)	7.6 (1.2 to 14.0)	22.9 (13.0 to 32.7)	23.9 (13.7 to 34.1)
OR vs placebo (95% CI)		3.8 (1.3 to 11.1)	4.1 (1.4 to 12.2)
P value		0.0119	0.0068

*Statistical analyses of primary and secondary endpoints at week 16 were adjusted for multiplicity. Additional endpoints were not controlled for multiple comparisons and nominal p values are reported.
†Response criteria of ≥0.35 improvement from baseline (minimum clinically important difference in PsA).
ACR, American College of Rheumatology; DAPSA, Disease Activity Index for Psoriatic Arthritis; HAQ-DI, Health Assessment Questionnaire-Disability Index; LEI, Leeds Enthesitis Index; MCS, Mental Component Summary; MDA, minimal disease activity; NA, not analysed; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI, Psoriasis Area and Severity Index; PCS, Physical Component Summary; PsA, psoriatic arthritis; SF-36, Short Form-36.

Table 3 Summary of safety

Adverse event (AE), n (%)	Placebo n=66	Deucravacitinib 6 mg once a day n=70	Deucravacitinib 12 mg once a day n=67
Total AEs	28 (42.4)	46 (65.7)	44 (65.7)
Treatment-related AEs	6 (9.1)	22 (31.4)	17 (25.4)
Deaths	0	0	0
Serious AEs	1 (1.5)	0	0
Treatment discontinuation due to AEs	1 (1.5)	3 (4.3)	4 (6.0)
AEs occurring in ≥5% of patients in any treatment group			
Nasopharyngitis	5 (7.6)	4 (5.7)	12 (17.9)
Upper respiratory tract infection	0	4 (5.7)	1 (1.5)
Sinusitis	0	0	5 (7.5)
Bronchitis	1 (1.5)	4 (5.7)	0
Headache	3 (4.5)	5 (7.1)	1 (1.5)
Rash	0	3 (4.3)	4 (6.0)
Diarrhoea	0	4 (5.7)	0

Includes events with a start date between the first dose and the week 16 visit date (inclusive), or between the first dose and 30 days after the last dose of study drug for patients who discontinued early.

or malignancy observed with deucravacitinib treatment at either dose. AEs that resulted in treatment discontinuation occurred in one patient in the placebo group (PsO), three patients in the deucravacitinib 6 mg once a day group (bronchitis, rash and rosacea) and four patients in the deucravacitinib 12 mg once a day group (furuncle, urticaria, mouth ulceration and multiple events in one patient: gastro-oesophageal reflux disease, nausea, dizziness, headache and increased blood pressure). No differences in mean change in laboratory parameters (haematology (lymphocyte, neutrophil, platelet and haemoglobin levels), serum lipids (total cholesterol and triglyceride levels) or chemistry (alanine aminotransferase, aspartate aminotransferase, creatine phosphokinase and creatinine)) were observed between deucravacitinib and placebo treatment arms across 16 weeks of treatment (figure 2 and online supplemental table S2). Majority of the patients had laboratory parameters within normal ranges (Common Terminology Criteria for Adverse Events grade 0) throughout the study; shifts to grades 3 or 4 from baseline, when treatment decisions would need to be made, were uncommon, with no clinically meaningful differences overall between the treatment arms (online supplemental table S3).

DISCUSSION

Deucravacitinib is an oral selective TYK2 inhibitor that targets the unique pseudokinase domain of the enzyme and inhibits TYK2-mediated pathways with high selectivity over other JAKs (JAK 1/2/3).[9] In this relatively small, phase II study, deucravacitinib given at two doses, 6 mg once a day and 12 mg once a day, showed higher responses than placebo in multiple domains of PsA, including arthritis, enthesitis, dactylitis and skin inflammation. Although a decrease in clinical efficacy in women compared with men has been observed in some other PsA trials,[22] a diminution in ACR-20 responses with deucravacitinib treatment in women versus men was not seen in this trial. In addition, significant improvements were observed in several patient-reported outcome measures, including physical function (HAQ-DI) and the quality of life measure SF-36 PCS, with deucravacitinib treatment. Differences from placebo were noted as early as week 4 for patient-reported outcomes and week 8 for ACR responses. Higher responses were also seen with deucravacitinib treatment versus placebo in SF-36 MCS and the composite measures of disease activity, PASDAS and DAPSA. The composite measure of low disease activity, MDA, is a treat-to-target goal in the treatment of PsA and reflects meaningful benefits across multiple disease domains in PsA.[23] A substantial proportion of patients (approximately 23%) were able to achieve MDA with deucravacitinib treatment versus placebo (7.6%) by week 16. The beneficial effects with deucravacitinib treatment overall did not appear to be dose-dependent, as comparable responses were observed in the two groups across a majority of endpoints (eg, LEI, HAQ-DI responders, SF-36 PCS and MCS change from baseline, PASDAS improvements from baseline, MDA). However, few endpoints, including PASI-75, ACR-50 and ACR-70, did exhibit numerical differences between dose groups at week 16.

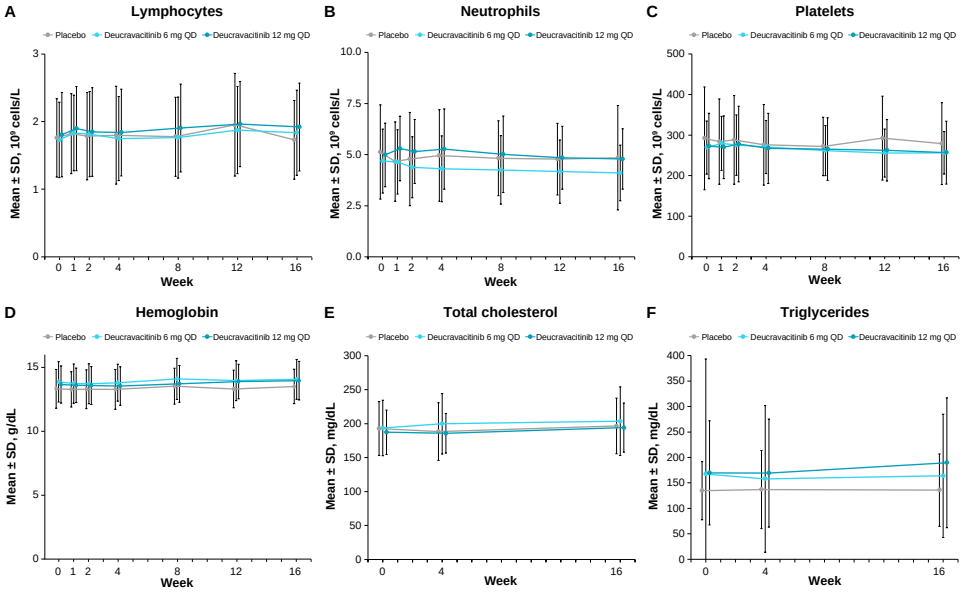

Figure 2 Laboratory parameters over 16 weeks (mean±SD): (A) lymphocytes, (B) neutrophils, (C) platelets, (D) haemoglobin, (E) total cholesterol and (F) triglycerides. Supporting values are shown in online supplemental table S5. QD, once a day.

Deucravacitinib was generally well tolerated in patients with PsA, and the safety profile was consistent with that previously described earlier in PsO studies.[14 15] AEs resulting in treatment discontinuation were few and were not specific to any organ system. The most common AE category was infections of the upper respiratory tract, which did not require treatment in the majority of cases and none led to discontinuation; this is consistent with the mechanism of action of deucravacitinib. Skin events of interest observed in the phase II PsO trial,[14] including acne and dermatitis acneiform, occurred more frequently in patients treated with deucravacitinib than with placebo in this phase II PsA trial; however, neither occurred in more than 3.0% of the patients in any deucravacitinib treatment arm in the current study. No cases of herpes zoster infection, tuberculosis, opportunistic infections, malignancies or thromboembolic events were observed in deucravacitinib-treated patients. Changes in laboratory measures that are commonly observed with inhibitors of JAK 1/2/3 and are clinically meaningful, such as in haematological parameters, lipid levels and chemistry parameters, were not observed with deucravacitinib treatment, demonstrating the selectivity for TYK2 versus JAK 1/2/3.[10]

The study has some limitations. The sample size was relatively small and the results are reported over only 16 weeks of treatment, which limit the generalisability of our findings.

In conclusion, selective inhibition of TYK2 with deucravacitinib is a promising therapeutic option for PsA. Deucravacitinib showed efficacy across multiple disease domains and patient-reported outcomes and has a safety profile that is consistent with its mechanism of action and with that observed in previous phase II and phase III trials in PsO.[14 15] Larger trials over longer durations are warranted to establish the long-term efficacy and safety profile of deucravacitinib in patients with active PsA.

PREVIOUS PUBLICATION

1. ACR Convergence (2020) American College of Rheumatology 2020 Annual Scientific Meeting. Mease PJ, *et al*. Efficacy and Safety of Deucravacitinib (BMS-986165), an Oral, Selective Tyrosine Kinase 2 Inhibitor, in Patients With Active Psoriatic Arthritis: Results From a Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial. Poster presentation: November 9, 2020.
2. EADV (2021) European Academy of Dermatology and Venereology – 30th Congress (Virtual). Mease PJ, *et al*. Efficacy of Deucravacitinib, an Oral, Selective Tyrosine Kinase 2 Inhibitor, in Musculoskeletal Manifestations of Active Psoriatic Arthritis in a Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial. Poster presentation: September 29, 2021.
3. CRA (2021) Chinese Rheumatology Association - 25th National Academic College of Rheumatology Conference. Mease P, *et al*. Efficacy and Safety of Deucravacitinib (BMS-986165), an Oral, Selective Tyrosine Kinase 2 Inhibitor, in Patients With Active Psoriatic Arthritis: Results From a Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial. Poster presentation: May 20, 2021.
4. EULAR (2021) European Alliance of Associations for Rheumatology - EULAR 2021. Mease PJ, *et al*. Efficacy of Deucravacitinib, an Oral, Selective Tyrosine Kinase 2 Inhibitor, in Musculoskeletal Manifestations of Active Psoriatic Arthritis in a Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial. Oral presentation: June 4, 2021.
5. EULAR (2021) European Alliance of Associations for Rheumatology - EULAR 2021. Mease PJ, *et al*. Efficacy and Safety of Deucravacitinib, an Oral, Selective Tyrosine Kinase 2 Inhibitor, in Patients With Active Psoriatic Arthritis: Results From a Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial. Poster presentation: June 4, 2021.
6. IFPA (2021) International Federation of Psoriasis Associations - 6th World Psoriasis & Psoriatic Arthritis Conference. Mease PJ, *et al*. Efficacy and Safety of Deucravacitinib, an Oral, Selective Tyrosine Kinase 2 Inhibitor, in Patients With Active Psoriatic Arthritis: Results From a Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial. Poster presentation: June 30, 2021.
7. JSPR (2021) Japanese Society for Psoriasis Research - 36th Annual Meeting. Habiro K, Mease PJ, *et al*. Efficacy and Safety of TYK2 Inhibitor Deucravacitinib in Patients With Active Psoriatic Arthritis: Global Phase 2 Clinical Study. Oral presentation: September 3, 2021.
8. DGRh (2021) Deutschen Gesellschaft für Rheumatologie - 49 Kongress. Mease PJ, *et al*. Efficacy and Safety of Deucravacitinib, an Oral, Selective Tyrosine Kinase 2 Inhibitor, in Patients With Active Psoriatic Arthritis: Results From a Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial. Poster presentation: September 15, 2021.

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CLINICAL SCIENCE

Persistence and effectiveness of the IL-12/23 pathway inhibitor ustekinumab or tumour necrosis factor inhibitor treatment in patients with psoriatic arthritis: 1-year results from the real-world PsABio Study

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ABSTRACT

Objective We evaluated real-world treatment persistence and effectiveness at 1 year following initiation of IL-12/23 inhibitor ustekinumab or a tumour necrosis factor inhibitor (TNFi) for psoriatic arthritis (PsA).

Methods PsABio (NCT02627768), a prospective, observational study, followed patients with PsA prescribed first-line to third-line ustekinumab or TNFi. Drug persistence, effectiveness (achievement of clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) low disease activity (LDA)/remission and minimal disease activity/very low disease activity (MDA/VLDA)), and safety were assessed every 6 months. In addition to descriptive statistics, propensity score (PS)-adjusted comparisons across cohorts were performed.

Results At 1 year, overall persistence was similar in the ustekinumab (n=317/438, 72.4%) and TNFi (n=321/455, 70.5%) groups. PS-adjusted HR (95% CI) for stopping/switching ustekinumab versus TNFi was 0.82 (0.60; 1.13). cDAPSA LDA (including remission)/remission was achieved in 55.9%/22.1% of ustekinumab-treated and 67.1%/31.7% of TNFi-treated patients; PS-adjusted ORs (95% CI) were 0.80 (0.57; 1.10) for cDAPSA LDA and 0.73 (0.49; 1.07) for remission. MDA/VLDA was achieved in 34.2%/11.9% of ustekinumab-treated and 43.1%/12.6% of TNFi-treated patients; PS-adjusted ORs (95% CI) were 0.89 (0.63; 1.26) for MDA and 0.90 (0.54; 1.49) for VLDA. The safety profiles were similar in both groups.

Conclusion In the real-world PsABio Study, after 1 year of treatment, although unadjusted persistence was numerically slightly higher for ustekinumab versus TNFi and unadjusted effectiveness was numerically slightly higher for TNFi versus ustekinumab, the PS-adjusted comparisons demonstrated comparable overall persistence, effectiveness and safety for both modes of action in PsA.

Key messages

What is already known about this subject?

⇒ Although many randomised controlled trials have demonstrated efficacy and safety of biologics in psoriatic arthritis (PsA), real-world data comparing them, particularly over the long term, are lacking.

⇒ The PsABio real-world observational study provided comparative data on ustekinumab and tumour necrosis factor inhibitors (TNFi) in PsA treatment over 6 months and indicated similar efficacy.

What does this study add?

⇒ We provide 1-year analyses from the PsABio Study.

⇒ Drug persistence was similar at 1 year following treatment initiation (72.4% with ustekinumab and 70.5% with TNFi).

⇒ Drug effectiveness and safety were also similar for ustekinumab and TNFi at 1 year.

How might this impact on clinical practice or future developments?

⇒ Efficacy, safety and persistence are important considerations when making treatment decisions in PsA.

⇒ These 1-year results from the PsABio Study provide real-world evidence on factors which may impact treatment selection and help inform treatment decisions in clinical practice.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic immune-mediated disease, affecting approximately 20%–30% of patients with psoriasis.[1 2] Patients may present with various musculoskeletal and other manifestations such as arthritis, enthesitis, dactylitis, spondyloarthritis, and skin and nail disease.[1]

Treatment options for PsA include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and disease-modifying antirheumatic drugs (DMARDs): conventional synthetic DMARDs; targeted synthetic DMARDs and biological DMARDs (bDMARDs).[3] As the interleukin (IL)-12, IL-23 and IL-17 axes are critical pathways in the pathogenesis of PsA,[4–6] bDMARDs directed against IL-12/IL-23 (p40), IL-23 (p19) and IL-17A, as well as tumour necrosis factor inhibitors (TNFi), have been shown to be effective.[6–8] Ustekinumab, a fully human IgG1 monoclonal antibody that inhibits

IL-12/IL-23,[9] was the first licensed non-TNFi bDMARD therapy in psoriasis and PsA and combines efficacy against disease activity in joints and skin with a favourable safety profile.[7 10 11]

Owing to the significant disease heterogeneity, number of available drugs and limited head-to-head clinical trials in PsA,[12 13] treatment selection is challenging. Treatment persistence is important when managing patients who require long-term treatment, in whom poor adherence (the degree of conformity to treatment recommendations relating to dose and frequency) and poor persistence can lead to suboptimal outcomes.[14 15] Research has shown that the main reasons for switching to a different biologic are lack of effectiveness and adverse events (AEs),[16–19] with patients who switched subsequently recording lower response rates and drug persistence than with their initial bDMARD.[16] Female sex, smoking,[15 17 20] presence of comorbidities[18 21] and higher number of prior therapies are factors associated with poor persistence.[17] Adherence, an influencing factor for persistence,[22] was found to be higher in patients with longer PsA duration (>9 years).[23 24] One study reported that 1-year continuation and low disease activity were predictive of 12-year persistence, indicating that better initial treatment adherence may lead to long-term persistence.[25]

Data on comparisons of different treatment modes of action are lacking in PsA.[19] A retrospective Swedish registry study with a maximum follow-up of 10.6 years demonstrated favourable persistence with ustekinumab versus adalimumab across treatment lines.[26]

Six-month data from the prospective, observational PsABio cohort study of ustekinumab and TNFi treatment in patients with PsA indicated that later line of treatment, female sex and comorbidities as well as baseline disease impact, high clinical disease activity, and chronic widespread pain were shown to negatively influence treatment response.[27]

Here we present data on persistence, the primary outcome of PsABio, as well as clinical effectiveness, disease impact and safety after 1 year of follow-up.

METHODS

Study design

PsABio (NCT02627768) is an observational, multinational study of patients with PsA treated with first-line to third-line ustekinumab or a TNFi by their rheumatologist, reflecting real-world practice. The study duration per participant was up to 3 years, with follow-up twice yearly. This 1-year analysis reports the first PsABio comparative drug persistence data, extended effectiveness outcomes regarding achievement of LDA or remission using clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) definitions and minimal disease activity/very low disease activity (MDA/VLDA) as well as the patient-reported 12-item Psoriatic Arthritis Impact of Disease (PsAID-12) measure, and safety data.

Patients

Adults with PsA, who required ustekinumab or any approved TNFi (including biosimilars; online supplemental table S1) as first-line, second-line or third-line treatment, were included.

Assessments

Persistence

Treatment persistence was defined as the time between initiation of bDMARD until last dose plus one dispensing interval or stop/switch to another bDMARD, or study withdrawal. For calculation of average persistence, data cut-off date for patients remaining on initial treatment was included.

cDAPSA and MDA/VLDA

cDAPSA were calculated based on the sum of four components: tender joint count for 68 joints (TJC68,), swollen joint count for 66 joints (SJC66) patient global assessment and patient pain, with scores ≤14 and ≤4 denoting cDAPSA LDA and remission, respectively.[28 29] MDA and VLDA were based on attaining five and seven, respectively, out of the following seven domain cut-offs: TJC68≤1; SJC66≤1; Leeds Enthesitis Index ≤1; skin involvement assessed as body surface area (BSA) ≤3%; Health Assessment Questionnaire Disability Index (HAQ-DI) score ≤0.5; patient global assessment ≤20 (Visual Analogue Scale (VAS) in mm); and patient pain VAS ≤15.[30]

Patient-reported disease impact measure PsAID-12

The PsAID-12 is a validated, self-administered, weighted questionnaire that assesses the impact of PsA on patients' lives.[31] Each question is answered using a numerical rating scale, from 0 (none/no difficulty/very well) to 10 (extreme/extreme difficulty/very poorly).

Safety

Details of AEs, serious AEs and AEs of special interest (for ustekinumab defined as malignancies, serious and opportunistic infections and serious neurological disorders) were collected from the first use of ustekinumab or a TNFi in the study. All AEs that started during initial and subsequent treatments in the risk window (defined as the time between treatment initiation and 91 days after treatment stop) were reported.

Statistical analyses

The sponsor (Janssen Pharmaceuticals NV, Beerse, Belgium) oversaw the development of the statistical plan, data validation and all statistical analyses.

Populations

The safety set included all patients with baseline and any available follow-up data. Analysis of persistence and effectiveness was based on the effectiveness set, comprising all patients with baseline data and any postbaseline effectiveness data up to the upper limit of the month 12 visit window, which is up to 15 months' follow-up (including patients who switched/stopped treatment due to AEs, lack of efficacy or other reasons). For patients whose last available assessment was earlier than the lower limit of the 12-month visit window, the end-point analysis used the last observation carried forward (LOCF).

Analyses

The analysis was exploratory. No predefined hypotheses were tested and no adjustment for multiplicity was applied. Observed values and changes from baseline of effectiveness outcomes (MDA/VLDA and cDAPSA LDA/remission) were summarised at each assessment time point. cDAPSA LDA always included remission and MDA always included VLDA. Between-group differences and changes over time were described using 95% CIs. Persistence for ustekinumab and TNFi was described by Kaplan-Meier statistics and log-rank test for the effectiveness set, as well as by relevant baseline subgroups.

In addition to the descriptive statistics, comparative analyses were performed to investigate the differences between treatment cohorts in terms of persistence and effectiveness, including propensity score (PS) adjustment for imbalanced baseline demographic and disease-related covariates. In these analyses, for patients who switched/stopped their initial treatment during

Table 1 Baseline demographics (effectiveness set; n=893)

	UST (n=438)	TNFi (n=455)
Age years	51.0 (12.5) (**49.9; 52.2**)	48.5 (12.5) (**47.3; 49.7**)
Female, n (%)	246 (56.2) (51.4; 60.9)	248 (54.5) (49.8; 59.1)
BMI, kg/m^2	28.6 (6.2) (27.9; 29.2)	27.7 (5.3) (27.2; 28.2)
Disease duration since initial diagnosis, years	7.5 (8.1) (6.7; 8.3)	6.2 (6.6) (5.6; 6.9)
Line of bDMARD treatment, n (%)		
First-line	197 (45.0) (**40.3; 49.8**)	251 (55.2) (**50.5; 59.8**)
Second-line	151 (34.5) (30.0; 39.1)	149 (32.7) (28.4; 37.3)
Third-line	90 (20.5) (**16.9; 24.6**)	55 (12.1) (**9.2; 15.4**)
csDMARD exposure, n (%)		
Previous exposure	384 (87.7) (84.2; 90.6)	421 (92.5) (89.7; 94.8)
Ongoing exposure at baseline	173 (39.5) (**34.9; 44.2**)	251 (55.2) (**50.5; 59.8**)
MTX exposure ongoing at baseline	131 (29.9) (**25.7; 34.4**)	191 (42.0) (**37.4; 46.7**)
Weekly MTX dose, mg	15.3 (5.5) (14.3; 16.3)	15.0 (4.6) (14.3; 15.7)
Other treatments exposure ongoing at baseline, n (%)		
NSAIDs	240 (54.8) (**50.0; 59.5**)	313 (68.8) (**64.3; 73.0**)
Glucocorticosteroids	143 (32.6) (28.3; 37.3)	156 (34.3) (29.9; 38.8)
Comorbidities present, n (%)	301 (68.7) (64.1; 73.0)	277 (60.9) (56.2; 65.4)
Cardiovascular disease/ metabolic syndrome*	184 (42.0) (37.3; 46.8)	162 (35.6) (31.2; 40.2)
Anxiety or panic disorders	18 (4.1) (2.5; 6.4)	18 (4.0) (2.4; 6.2)
Depression	40 (9.1) (6.6; 12.2)	29 (6.4) (4.3; 9.0)
GI disease or medical history of IBD	55 (12.6) (9.6; 16.0)	49 (10.8) (8.1; 14.0)
FiRST score suggestive of chronic widespread pain (scores ≥5)	163 (39.0) (**34.3; 43.9**)	126 (29.4) (**25.2; 34.0**)

Data are mean (SD) (95% CI of the mean) unless otherwise stated; % is that of available data. Variables in bold indicate non-overlapping 95% CI.
*Hypertension, myocardial infarction, congestive heart failure, stroke or transient ischaemic attack, peripheral vascular disease, hyperlipidaemia, type 1 or type 2 diabetes or angina pectoris.
bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; FiRST, Fibromyalgia Rapid Screening Tool; GI, gastrointestinal; IBD, inflammatory bowel disease; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

the 12-month observation period, the LOCF effectiveness end points were imputed as non-responders for binary end points, or as showing no improvement from baseline for continuous end points.

RESULTS

Patients

A total of 991 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. For this 1-year analysis, 893 patients were included in the effectiveness analysis set (ustekinumab n=438; TNFi n=455) and 927 patients in the safety set (ustekinumab n=457; TNFi n=470; online supplemental figure S1). Of the 438 patients receiving ustekinumab, 341 (77.9%) were on a 45 mg dose, 96 (21.9%) were on a 90 mg dose and 1 (0.2%) patient was on another dose.

Demographics, baseline/clinical characteristics

Patients in the ustekinumab group were older, had more comorbidities and were more likely to have had previous bDMARD exposure, but fewer patients were on concurrent methotrexate (MTX) and NSAIDs than those in the TNFi group. Ustekinumab was given as first-line treatment in 45.0%, second-line in 34.5% and third-line in 20.5% of patients versus 55.2%, 32.7% and 12.1% on TNFi, respectively (table 1). More patients in the ustekinumab versus TNFi group had severe skin involvement as assessed by BSA at baseline (table 2). Details regarding the types of previous bDMARD treatments are provided in online supplemental table S2.

Table 2 PsA clinical characteristics at baseline (effectiveness set)

PsA characteristics	UST (n=438)	TNFi (n=455)
Psoriasis BSA, n (%)		
Clear/almost clear skin	102 (28.7) (24.1; 33.7)	116 (33.0) (28.1; 38.1)
<3% but not clear/almost clear skin	34 (9.6) (6.7; 13.1)	53 (15.0) (11.5; 19.2)
3–10%	124 (34.9) (30.0; 40.1)	131 (37.2) (32.2; 42.5)
>10%	95 (26.8) (**22.2; 31.7**)	52 (14.8) (**11.2; 18.9**)
Axial involvement* – pure or combined with peripheral, n (%)	153 (35.8) (31.3; 40.6)	166 (37.4) (32.9; 42.1)
Oligoarticular†, n (%)	96 (22.5) (18.6; 26.7)	129 (29.1) (24.9; 33.5)
Polyarticular‡, n (%)	286 (67.0) (62.3; 71.4)	283 (63.7) (59.1; 68.2)
SJC66	5.9 (8.2) (5.1; 6.8)	5.8 (7.5) (5.1; 6.6)
TJC68	12.5 (12.7) (11.2; 13.8)	11.0 (10.5) (9.9; 12.0)
cDAPSA, n (%)	30.6 (20.2) (28.5; 32.7)	29.3 (18.6) (27.3; 31.2)
Remission	10 (2.8) (1.3; 5.1)	7 (2.0) (0.8; 4.0)
Low	36 (10.1) (7.1; 13.6)	39 (11.0) (7.9; 14.7)
Moderate	141 (39.4) (34.3; 44.7)	149 (41.9) (36.7; 47.2)
High	171 (47.8) (42.5; 53.1)	161 (45.2) (40.0; 50.6)
MDA§, n (%)	16 (4.3) (2.5; 7.0)	18 (5.1) (3.0; 7.9)
VLDA, n (%)	1 (0.3)(0.0; 1.4)	2 (0.5) (0.1; 2.0)
Enthesitis¶, n (%)	192 (47.8) (42.8; 52.8)	204 (51.3) (46.2; 56.3)
Dactylitis**, n (%)	74 (17.7) (14.1; 21.7)	90 (21.8) (17.9; 26.1)
PsAID-12 total score	5.8 (2.1) (5.5; 6.0)	5.5 (2.1) (5.3; 5.7)
HAQ-DI	1.1 (0.7) (1.1; 1.2)	1.2 (0.7) (1.1; 1.2)

Data are mean (SD) (95% CI of the mean) unless otherwise stated; % is that of available data. Variables in bold indicate non-overlapping 95% CI.
*Pure axial PsA is defined as having only axial involvement (presence of axial disease declared by the treating rheumatologist without requirement for imaging), while combined axial PsA includes axial involvement and at least one of the following: distal interphalangeal joint involvement, monoarticular or oligoarticular PsA, polyarticular PsA, and arthritis mutilans. 2.1% of patients in the UST group and 3.2% in the TNFi group had pure axial PsA with inflammatory back pain.
†Either TJC68 and SJC66 are both non-missing and patient has <5 swollen or <5 tender joint counts, or in case TJC68 and/or SJC66 are missing monoarticular or oligoarticular PsA is indicated by the investigator.
‡Either TJC68 and SJC66 are both non-missing and patient has ≥5 swollen and ≥5 tender joint counts, or in case TJC68 and/or SJC66 are missing polyarticular PsA is indicated by the investigator.
§MDA includes VLDA.
¶Enthesitis presence defined as Leeds Enthesitis Index ≥0.
**Dactylitis presence on assessment of hands and feet.
BSA, body surface area; cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; HAQ-DI, Health Assessment Questionnaire Disability Index; MDA, minimal disease activity; PsA, psoriatic arthritis; PsAID-12, 12-item Psoriatic Arthritis Impact of Disease; SJC66, swollen joint count for 66 joints; TJC68, tender joint count for 68 joints; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab; VLDA, very low disease activity.

Persistence

Persistence on ustekinumab and TNFi was similar at 1 year (±3 months) (figure 1A), with 72.4% of ustekinumab-treated and 70.5% of TNFi-treated patients remaining on their initial treatment. Patients stopped/switched treatment predominantly due to lack of effectiveness (ustekinumab 76.9%; TNFi 69.4%) or safety/AEs (ustekinumab 12.4%; TNFi 28.4%); others switched due to patient's/physician's preference, access to the drug or for guideline reasons. The PS-adjusted Cox persistence analysis confirmed the observed finding: ustekinumab versus TNFi HR (95% CI) for stopping/switching bDMARD was 0.82 (0.60; 1.13). The overall observed mean time on drug was 13.1 months (SD 3.5) for patients receiving ustekinumab versus 12.7 months (SD 4.2) for patients receiving a TNFi (a breakdown of treatment durations for individual TNFi is provided in online supplemental table S3).

Gender

Overall, as well as within both treatment cohorts, shorter drug persistence was observed in women than men (figure 1B).

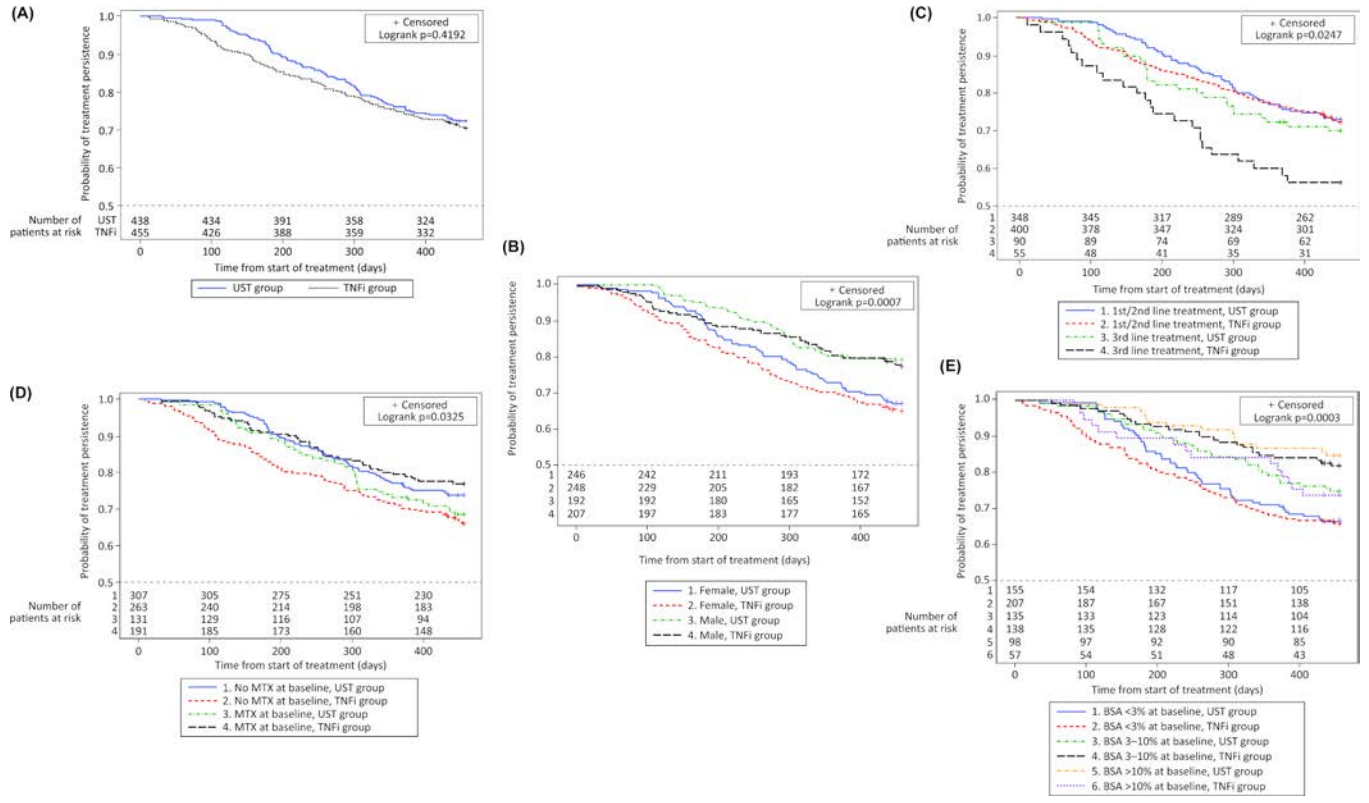

Figure 1 Kaplan-Meier plots of treatment persistence with ustekinumab versus TNFi (A) Overall, (B) By sex, (C) By treatment line, (D) By presence/absence of methotrexate and (E) By extent of skin involvement at baseline. BSA, body surface area; MTX, methotrexate; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

Comparing the treatment cohorts by means of a PS-adjusted Cox persistence analysis, no interaction was observed of the factor sex and the treatment cohort.

Axial involvement

PS-adjusted Cox analysis showed no difference in persistence between ustekinumab versus TNFi (HR: 0.83 (95% CI 0.50; 1.38)) for patients with axial involvement (defined as presence of axial disease declared by the treating rheumatologist without requirement for imaging) at baseline.

bDMARD line

Although the PS-adjusted Cox proportional hazard model did not show an overall significant interaction between the treatment lines and the treatment cohorts, the Kaplan-Meier graphs clearly showed better drug persistence in patients with first-line/second-line treatment than in patients with third-line treatment, with TNFi third-line treatment being associated with numerically shorter persistence than all other lines including ustekinumab third-line treatment (figure 1C).

Monotherapy

The observed better persistence on ustekinumab monotherapy versus TNFi monotherapy (figure 1D) was confirmed in the PS-adjusted Cox persistence analysis that showed a ustekinumab versus TNFi HR (95% CI) of 0.61 (0.42; 0.90). In patients co-treated with MTX, the observed ustekinumab and TNFi difference in persistence was not confirmed in the PS-adjusted Cox model (HR: 1.37; 95% CI 0.83; 2.26). There was no notable difference in the mean weekly MTX dose between ustekinumab and TNFi treatment groups (15.3 mg (SD 5.5) and 15.0 mg (SD 4.6), respectively).

Skin involvement

In the observed analysis, patients with more skin involvement at baseline persisted longer on their biologic than those with less skin involvement, in particular on ustekinumab (figure 1E). This was partly confirmed in the PS-adjusted Cox persistence analysis that showed a trend (p=0.0632) towards an interaction between the factor skin involvement and the treatment cohort, with longer persistence on ustekinumab in patients with baseline BSA >10% (HR: 0.41; 95% CI 0.19; 0.89).

Effectiveness

The observed proportion of patients achieving cDAPSA LDA/remission at 1 year was 55.9%/22.1% for the ustekinumab group and 67.1%/31.7% for the TNFi group; PS-adjusted ORs (95% CI) for ustekinumab versus TNFi were 0.80 (0.57; 1.10) for cDAPSA LDA and 0.73 (0.49; 1.07) for cDAPSA remission. Across all lines of treatment, the observed proportion of patients achieving MDA/VLDA was 34.2%/11.9% in the ustekinumab group and 43.1%/12.6% in the TNFi group (figure 2); PS-adjusted ORs (95% CI) for ustekinumab versus TNFi treatment were 0.89 (0.63; 1.26) for MDA and 0.90 (0.54; 1.49) for VLDA. The proportion of patients on ustekinumab or TNFi who achieved MDA at 6 months and 12 months is shown in figure 3.

PsAID-12

From baseline to 1 year, both treatments improved disease impact measured by PsAID-12 (total and individual domain scores) (figure 4), with the majority of the improvement occurring by month six in both cohorts. PS-adjusted treatment comparison between the ustekinumab and TNFi groups showed similar improvement in total PsAID-12 (regression coefficient (0.14, 95% CI −0.22; 0.51), and in individual domains, except skin

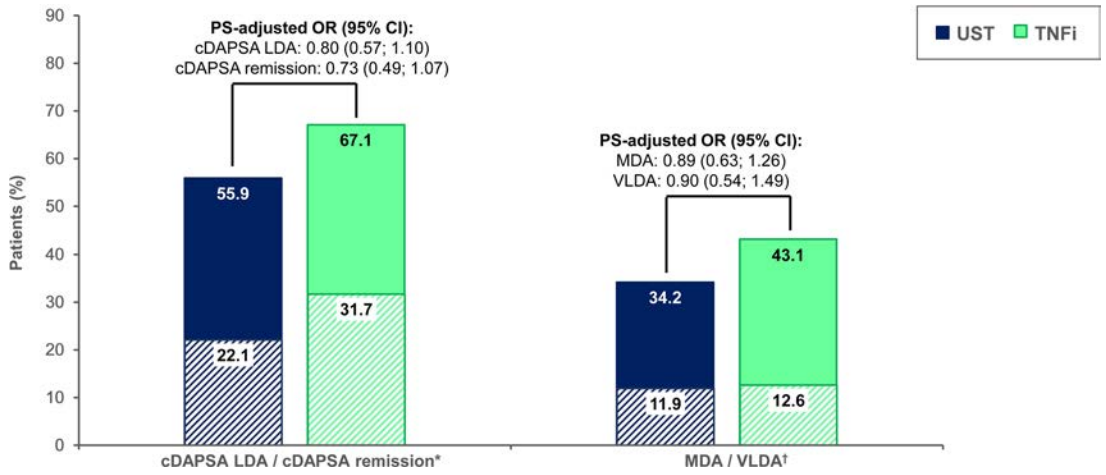

Figure 2 Disease outcomes at month 12 for patients with PsA receiving ustekinumab or TNFi. *Main (solid) bar represents cDAPSA LDA (including remission; cDAPSA ≤13) and inset (hashed) bar represents cDAPSA remission ≤4. †Main (solid) bar represents MDA (including VLDA) and inset (hashed) bar represents VLDA. cDAPSA, clinical disease activity in psoriatic arthritis; LDA, low disease activity; MDA, minimal disease activity; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitor; VLDA, very low disease activity.

problems, where more improvement was observed with ustekinumab than TNFi (−0.55, 95% CI −1.04; −0.06). Within both groups, improvements in PsAID-12 and HAQ-DI showed moderate/strong positive correlation (ustekinumab: r=0.63, TNFi: r=0.70). Non-clinical aspects of PsAID-12, for example, difficulties participating in social activities and overall coping, improved with both treatments (online supplemental table S4).

Safety

At least one AE was reported for 24.4% of all patients receiving ustekinumab and 28.7% of patients receiving a TNFi, with 4.5% and 3.4%, respectively, reporting at least one serious AE. Three patients reported at least one serious infection in both treatment groups; there were three cases of pneumonia in patients receiving a TNFi and one case each of cellulitis, skin infection and staphylococcal bacteraemia in the ustekinumab group. A similar proportion of patients reported malignancies (excluding non-melanoma skin cancer; ustekinumab: n=4; TNFi: n=3, all single events) within the first year. Non-melanoma skin cancer was reported in two ustekinumab-treated and two TNFi-treated patients. Cardiovascular AEs were reported by two ustekinumab-treated and six TNFi-treated patients over 1 year but none were major and all were arrhythmias. Of note, all but two patients experiencing cardiovascular AEs had a medical history of cardiovascular disease/metabolic syndrome. During the first year of the study, an unexplained sudden death occurred in one patient in the ustekinumab group, and one patient in the TNFi group died due to pneumonia (online supplemental table S5).

DISCUSSION

The prospective PsABio study aims to provide comparative real-world data on treatment persistence of biologic therapy in patients with PsA. After 1 year of follow-up, drug persistence was similar for ustekinumab or a TNFi in the PS-adjusted analysis, although observed data showed slightly better persistence for ustekinumab versus TNFi. These results are in contrast to the results from recent retrospective database studies showing that patients with PsA who initiated IL-12/23 inhibitor treatment had

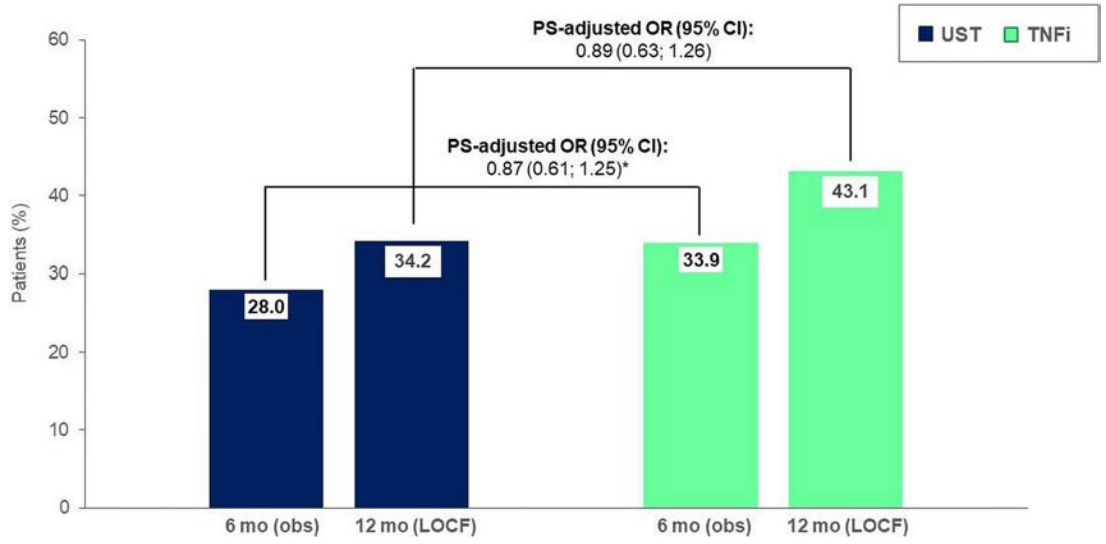

Figure 3 Proportion of patients achieving MDA at month 6 (observed) and month 12 (LOCF) and PS-adjusted ORs. *The 6-month PS-adjusted OR 95% CI are from the 6-month analysis. LOCF, last observation carried forward; MDA, minimal disease activity; mo, month; obs, observed; PS, propensity score.

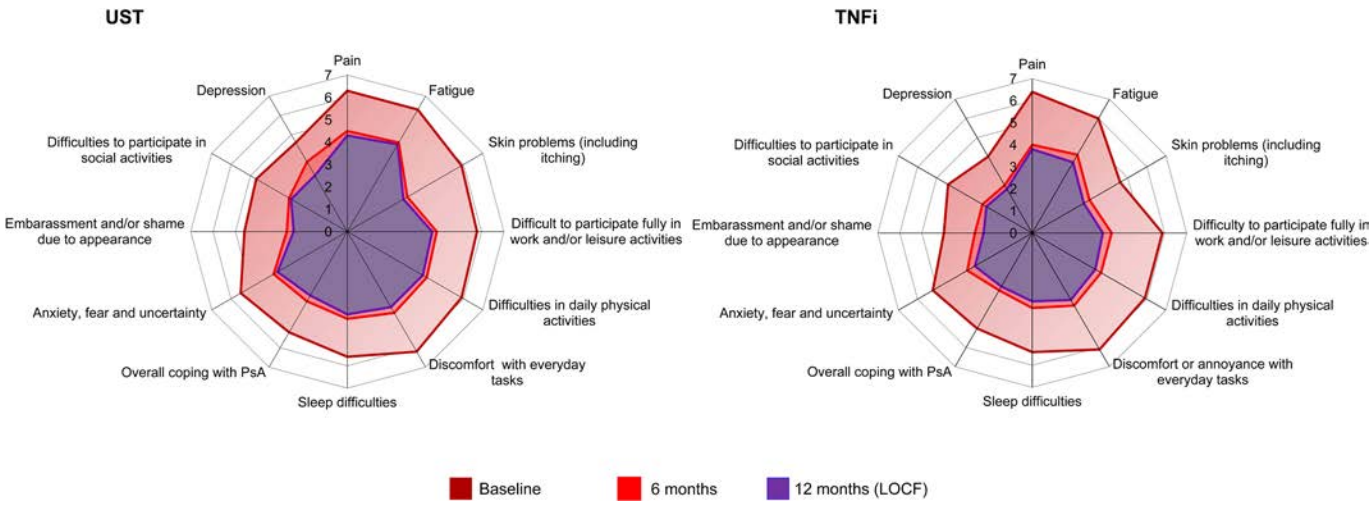

Figure 4 Mean PsAID-12 overall and domain scores at baseline and 1 year with ustekinumab (n=438) and TNFi (n=455). UST: mean (95% CI) total score improved from 5.8 (5.5; 6.0) at baseline to 3.9 (3.6; 4.1) at 6 months and 3.7 (3.4; 3.9) at 1 year. TNFi: mean (95% CI) total score improved from 5.5 (5.3; 5.7) at baseline to 3.4 (3.2; 3.7) at 6 months and 3.1 (2.9; 3.4) at 1 year. LOCF, last observation carried forward; PsA, psoriatic arthritis; PsAID-12, 12-item Psoriatic Arthritis Impact of Disease; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

significantly longer treatment persistence and lower discontinuation rates compared with those initiating a TNFi during 1 year follow-up[32] and those initiating adalimumab during 10 years follow-up.[26] Likewise, the subgroup of patients with PsA in the PSOLAR Study, a registry study of 12 095 patients with psoriasis, showed better drug persistence with ustekinumab versus TNFi.[19] This difference in results of adjusted analyses between the PsABio Study and the other studies could be due to various reasons: prospective non-interventional study setting, as done here, is different from retrospective claims database or registry analysis; the ustekinumab population in the current study was heavily affected by comorbidities, chronic widespread pain, late lines of bDMARD treatment, which may have impacted drug persistence with ustekinumab in this prospective patient cohort versus the other studies, and these or additional non-assessed imbalances may not have been fully adjusted for. Also, in this study in PsA, active psoriasis was not required and many patients had clear or almost clear skin, potentially reducing the advantage of ustekinumab treatment compared with TNFi.

The current study also showed lower drug persistence in women versus men with both treatments. Third-line TNFi treatment was associated with more reduced persistence than all other lines including third-line ustekinumab treatment. This observation supports previous reports, and the strategy of changing the biologic treatment mode of action, instead of cycling through treatments with the same pathophysiological target.[11 17 19]

Minimal or no skin involvement was strongly associated with low persistence in both cohorts. Patients with the greatest skin involvement at baseline showed longer persistence in both treatment groups, although persistence with TNFi was shorter than with ustekinumab in patients with BSA >10%, which may indicate the importance of skin improvement for patients. This effect is also seen with a greater improvement in PsAID-12 score in patients with higher baseline BSA. These observations are consistent with other studies showing a relationship between skin involvement and treatment persistence in PsA. This is expected, as the burden of psoriasis can significantly impact morbidity, and patients' health-related quality of life depends on successful treatment of skin symptoms.[33]

The differential importance of MTX co-therapy on persistence with ustekinumab versus TNFi demonstrated in this real-world study supports results from the long-term SPIRIT-H2H extension randomised controlled trial data.[12] While ustekinumab persistence is independent of co-therapy with MTX, TNFi persistence without MTX is shorter than with MTX and shorter than ustekinumab with/without MTX. This may be interpreted as a function of several mechanisms: patients receiving a TNFi may develop neutralising antidrug antibodies when MTX is not given; with ustekinumab, the risk of such antidrug antibodies is described as minimal.[34] Other reasons may include MTX co-therapy with TNFi being more effective for skin involvement and likely selection bias in this real-world study as more patients on TNFi versus ustekinumab were on MTX at baseline.

PS-adjusted treatment effectiveness (cDAPSA LDA/remission or MDA/VLDA) was not different for TNFi and ustekinumab at 6 months and 1 year although the observed proportions were higher with TNFi versus ustekinumab. Also, PsAID-12 scores improved in all domains between baseline and 1 year with both treatments.

Both ustekinumab and TNFi treatment have a favourable safety profile in this real-world study of patients with PsA presenting with several comorbidities. Although reported AEs and serious AE rates were similar for both groups, more patients in the TNFi group stopped/switched treatment due to AEs than in the ustekinumab group; at the same time more patients in the ustekinumab versus TNFi group stopped/switched due to lack of efficacy.

We did not evaluate outcomes in the individual dose groups of ustekinumab versus the TNFi group, as some patients received doses that were too high or too low relative to their body weight (in particular, obese patients weighing just over 100 kg). Moreover, some rheumatologists may have used a lower dose when the patient's disease was better controlled or escalated the dose when disease activity was less well controlled; therefore, analysis of different dose groups may introduce bias. Similar complexities of dosing also apply to TNFi.

PsABio is the only prospective real-world study comparing biologics with different modes of action in patients with PsA. The prospective open design allows the analysis and publication of data as they accumulate, permitting early detection of differences. The study captures data from a real-world population across eight different countries, each with their own local

guidelines and treatment preferences; data which will apply to routine patient care and management. The limitation is that the comparison between treatment cohorts had to be based on PS adjustment and not on randomisation, due to a probable selection bias in treatment choice.

This study has confirmed the strong impact of treatment line, gender and baseline extent of skin disease on persistence and demonstrated the effectiveness of ustekinumab or TNFi-based treatments in PsA, not only on physician-derived but also patient-reported outcomes, such as disease impact. The final 3-year data from the PsABio study may provide further insights, such as information about factors that may predict long-term persistence at an early stage of treatment.

CONCLUSION

Real-world results from the PsABio Study have demonstrated generally comparable drug persistence, efficacy and safety following 1 year of treatment with ustekinumab or a TNFi, after PS adjustment for counteracting imbalanced baseline characteristics caused by channelling bias. Patients in this study were more likely to remain on ustekinumab than TNFi when extensive skin disease was present and when MTX was not used as concomitant treatment. On unadjusted analysis, women had lower treatment persistence with both treatments versus men, indicating they may require more comprehensive multidimensional therapy.

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CLINICAL SCIENCE

Factors predicting axial spondyloarthritis among first-degree relatives of probands with ankylosing spondylitis: a family study spanning 35 years

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ABSTRACT

Objective Factors predicting axial spondyloarthritis (axSpA) among first-degree relatives (FDRs) of ankylosing spondylitis (AS) patients need to be defined. We investigated the predictive value of the probands' HLA-B27 and radiographic sacroiliitis status on disease occurrence among their FDR. We also assessed the predictive value of features of the clinical history, including chronic inflammatory back pain (CIBP) and acute anterior uveitis (AAU), among the FDR and how they can be used to improve classification and diagnosis of axSpA.

Methods In 1985, we studied 363 AS probands and 806 FDR who underwent rheumatologic examination, completed questionnaires, provided blood samples for HLA-typing and underwent radiography of sacroiliac joints. At follow-up in 2018–2019, 125 patients and 360 FDR were available for study, and completed a postal questionnaire about axSpA features. FDRs were asked to report whether after 1985 they had been diagnosed by Swiss rheumatologists as having axSpA.

Results Among HLA-B27(+) FDR, axSpA occurred in 25.4%–26.3%, independent of the radiographic sacroiliitis status of the proband. AAU occurred in 13/34 (38.2%) FDR with axSpA vs 29/251 (11.6%) FDR without axSpA (p=0.00004, OR=4.74 95% CI 2.15 to 10.47). The presence of CIBP at baseline did not predict later occurrence of axSpA but combining CIBP and pain/discomfort at the thoracic spine *and* at anterior (ventral) chest wall ever, assessed at follow-up in 2018–2019, provided 83.1% sensitivity and 87.2% specificity for current axSpA.

Conclusion Occurrence of AAU among FDR of axSpA probands should prompt screening for axSpA. Moreover, co-occurrence of CIBP and pain/discomfort in the thoracic spine and at anterior chest wall as a three-question tool may further enhance clinical suspicion of axSpA among these FDR.

Key messages

What is already known about this subject?

⇒ Familial occurrence of ankylosing spondylitis is well known, but factors predicting axial spondyloarthritis (axSpA) occurrence among first-degree relatives (FDR) are less well identified.

What does this study add?

⇒ Occurrence of chronic inflammatory back pain (CIBP) in FDR of axSpA probands is not a reliable predictor of later development of axSpA. However, occurrence of acute anterior uveitis and/or a combined occurrence of CIBP and pain/discomfort in the thoracic spine and at anterior chest wall, enhance early clinical suspicion and early diagnosis of axSpA among FDR of axSpA patients.

⇒ 'Healthy' HLA-B27(+) FDR may have unnoticed 'hidden' axSpA, in particular if they have thoracic complaints in the absence of CIBP.

How might this impact on clinical practice or future developments?

⇒ A three-question tool combining pain and discomfort at lumbar spine, thoracic spine and anterior chest wall has high sensitivity (83.1%) and specificity (87.2%). However, this triad needs to be fully validated as a potential diagnostic tool.

INTRODUCTION

The high familiality of ankylosing spondylitis (AS) is well established.[1–3] The prevalence of AS is considerably higher among HLA-B27(+) first-degree relatives (FDR) of patients with the disease compared with HLA-B27(+) persons from the general population.[4 5] This points to an important role of additional MHC genes, such as HLA-B60, and many non-MHC genes in contributing to disease susceptibility.[6 7]

Nowadays, the notion of AS has changed with increased emphasis on early diagnosis at its non-radiographic phase.[8 9] This has led to the concept of axial spondyloarthritis (axSpA), comprising both radiographic axSpA (AS defined by the modified New York (mNY) criteria[10] and non-radiographic axSpA (nr-axSpA). Whether the recurrence risk in relatives of axSpA patients varies according to the radiographic status of the proband is unknown. With nr-axSpA reported to be 2–3 times[11] more prevalent than AS itself, there is a significant clinical need to determine this risk rate, not the least for counselling and screening purposes.

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We have recently completed a family study spanning 35 years, the longest longitudinal study in axSpA to date. Here, we report features from patients' clinical history that best predict presence of axSpA for the large number of FDR who developed the disease during these 35 years. We evaluated whether presence at early age of chronic inflammatory low back pain (CIBP) and occurrence of features of acute anterior uveitis (AAU) are associated with onset of axSpA.

METHODS

Here the term 'axSpA' comprises the full spectrum of axSpA, that is, both radiographic (AS defined by the mNY criteria) and nr-axSpA.[10]

First phase of the study

In 1985, all members of the nation-wide Swiss Ankylosing Spondylitis Patient Society were invited to participate in the family study together with their spouses and FDR. These relatives were invited irrespective of whether they were known to have any rheumatic disease. The study was performed in centres spread all over the country.

A total of 1178 persons consented to participate and completed questionnaires on disease manifestations. They also underwent physical examination of axial and peripheral joints by a rheumatologist. Peripheral blood nucleated cells (PBNCs) were stored for HLA-typing and subsequent genetic analysis. Furthermore, to assess the presence of sacroiliitis, consenting non-pregnant participants, aged 18 and over, underwent pelvic radiography unless a recent radiograph was available. Pelvic radiographs were available for 360 of the 363 probands; the three probands with missing pelvic radiographs were excluded in this analysis.

Each sacroiliac (SI) joint on pelvic radiographs (total number 1081) was 'blindly' assessed twice by each of 4 experienced readers, that is, 8 (occasionally 9) times. The radiographs of 163/360 probands and 22/713 FDR were only available on-site for a few hours at the time of participant's physical examination in the local hospital, and therefore, could only be assessed once. Overall, 17.2% of the 1081 radiographs were read once, 0.4% 2–4 times, 3.2% 5–7 times and 79.2% 8–9 times. The sacroiliitis score ranged from 0 (normal) to 4 (ankylosis) for each SI joint assessment by a reader as per the mNY scoring system.[10] All scores for a single SI joint were added and divided by the number of assessments (range 1–9). Scores below bilateral grade 2.0 or unilateral grade 3.0 were considered not fulfilling the mNY criteria. Interobserver and intraobserver reliability were assessed by evaluating a subset of 243 pelvic films. Observers read films twice in sets of 40–50 radiographs. The interval between both readings was ≥7 days. The interobserver and intraobserver reliability coefficients were 0.865 and 0.903, respectively.

In 1986, all participants were informed by a letter about their individual HLA-B27 test result and radiographic findings of the SI joints.

Follow-up study

The former participants were asked to complete a 157-item postal questionnaire on manifestations of AS. The questionnaire dealt particularly with current or past symptoms at lumbar and gluteal region, thoracic spine and front part of the chest, and also addressed symptoms suggesting episodes of AAU. The next decisive step to perform the follow-up study was to determine whether the former 1178 participants were still alive and, if so, to trace their current postal addresses. Starting in April 2018, up to five mailings to a large number of Swiss city or village administrations were needed to obtain as much as possible up-to-date current addresses.

In the spring of 2019, letters providing detailed information about the follow-up study were sent to supposedly correct addresses. Participants who had provided written informed consent for genetic analysis of PBNCs were mailed the postal questionnaire, and those who did not return the questionnaire were mailed a reminder. The last questionnaires were returned in December 2019. Data were coded and anonymously stored in an Excel database.

Ascertainment of diagnosis

The diagnosis AS in the first phase of the study in 1985 was based on the clinical findings and the evaluation of the pelvic radiographs. Probands were categorised according to the mNY criteria, and their FDR were considered to have AS if they met the mNY criteria.

In the follow-up study (2019), recent imaging of the SI joints was mostly unavailable for us to establish whether the FDR who reported having been diagnosed (between 1986 and 2019) by their Swiss rheumatologists to have axSpA met the mNY criteria or had nr-axSpA. Therefore, we considered all new cases in the follow-up study to be suffering from axSpA, that is, they may have either radiographic axSpA or nr-axSpA.

Statistical analysis

Counts were compared by χ^2 testing. The test results are expressed as p values. OR were calculated with 95% CI.

Patient and public involvement

Two patients/coauthors were fully involved in the study.

RESULTS

Altogether 1178 persons, including 363 probands, participated in the first (1985) phase of the study of whom 485 consenting persons could be retrieved for the 2018–2019 follow-up study (125 probands and 360 FDR). Altogether 162 former participants (123 probands and 39 FDR) were known to have died; information about causes of death was not available. Demographic data of the 485 participants who were available and consented to participate in the follow-up study are shown in table 1, together with their radiographic and HLA-B27 status (figure 1). At baseline (1985) 84/125 (67.2%) probands met mNY criteria, 41 were categorised as nr-axSpA.

Occurrence of axSpA among FDR

The risk to develop axSpA for HLA-B27(+) FDR of HLA-B27(+) probands is considerable. At follow-up (2018–19) 42/162 HLA-B27(+) FDR had been diagnosed as having the disease, that is, an incidence of 25.9%; 95%CI 19.2% to 32.6%. The sex ratio was about equal: 17/67 (25.4%) HLA-B27(+) males and 25/95 (26.3%) HLA-B27(+) females. In contrast, 1/141 (0.7%) of HLA-B27(-) FDR of HLA-B27(+) probands and 1/29 (3.4%) HLA-B27(-) FDR of HLA-B27(-) probands (a son of a nr-axSpA proband) were diagnosed as having axSpA. The first mentioned HLA-B27(-) axSpA case comprises a sister of an HLA-B27(+) proband with nr-axSpA.The HLA-B27 and radiographic sacroiliac status of the proband of a third HLA-B27(-) case (a female) is unknown. Of the 42 HLA-B27(+) cases, 7 had radiographic sacroiliitis in 1985, the remaining 35 either had negative pelvic X-rays or did not undergo radiographic examination of their SI joints at baseline because they were pregnant or <18 years of age at that time. Thus, the diagnosis axSpA of these 35 FDR has

Table 1 Demographic data of axSpA probands and relatives participating in the 2019 Swiss Ankylosing Spondylitis Follow-up Family Study by HLA-B27 status and presence of sacroiliitis by New York criteria*

	No	Males	Females	Mean age (yr) (2019)	Age SD
All participants	485	238	247	64.56	9.73
All axSpA probands	125†‡§	78‡	47§	72.78	7.31
HLA-B27 positive axSpA Probands	*110*	*73*	*37*	*72.51*	*7.16*
Sacroiliitis present (1985)	79	54	25		
Sacroiliitis absent	31	19	12		
HLA-B27 negative axSpA probands	*13*	4	*9*	*75.54*	*8.68*
Sacroiliitis present (1985)	3	2	1		
Sacroiliitis absent	10	2	8		
All relatives	360	160	200	61.70	8.84
All relatives with axial SpA	45	18	27	58.02	8.04
HLA-B27 positive relatives	42	17	25	57.72	8.18
Sacroiliitis present (1985)	7	3	4		
Sacroiliitis absent (1985)	28	12	16		
Sacroiliitis unknown	7	2	5		
HLA-B27 negative relatives	3	1	2	62.0	5.29
Sacroiliitis absent (1985)	3	1	2		
All healthy relatives	315¶	142	173	62.20	8.81
Healthy relatives of HLA-B27 +Probands	262	118	144	62.07	9.17
HLA-B27 positive relatives	120	50**	70††	61.26	8.94
HLA-B27 negative relatives	140	66‡‡	74§§	62.87	9.25
HLA-B27 unknown relatives	3	2¶¶	0	55.50	14.85
Healthy relatives of HLA-B27- probands	29	16	13	60.76	6.66
HLA-B27 positive relatives	0				
HLA-B27 negative relatives	29	16	13	60.76	6.66
Healthy relatives of HLA-B27? probands	24	8	16	65.34	6.00
HLA-B27 positive relatives	9	4	5	68.12	5.69
HLA-B27 negative relatives	15	4	11***	63.67	5.39

New York criteria (grade 2 or higher bilaterally, or grade 3 or 4 unilaterally).
*Sacroiliitis: pelvic radiography from 1985 AS Family Study showing sacroiliitis by modified.
†Altogether 84 (67.2%) probands met modified New York criteria, 41 were categorised as nr-axSpA.
‡Unknown HLA-B27 status of one male proband with sacroiliitis.
§Unknown HLA-B27 status of one female proband with sacroiliitis.
¶HLA-B27 status of the probands of two FDR unknown (one relative HLA-B27(-); one relative HLA-B27(+)).
**No pelvic radiograph available for five males.
††No pelvic radiograph available for 11 females.
‡‡No pelvic radiograph available for four males.
§§No pelvic radiograph available for five females.
¶¶ No pelvic radiograph available for one male
***No pelvic radiograph available for two women.
AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; FDR, first-degree relatives.

been established at some point in time *between* 1986 and 2019. For two of these 35 FDR, recent radiographs were available that confirmed AS by mNY criteria, but for the other 33 FDR no recent imaging of the SI joints were available for us to review at follow-up. Of note, based on the responses to the questionnaire, 38 of all 42 (90.5%) HLA-B27(+) FDR with axSpA fulfilled the ASAS classification criteria for axSpA.[12 13]

Relationship with radiographic status of proband

In total 37 (88.1%) of the 42 HLA-B27(+) axSpA probands of the 42 HLA-B27(+) affected FDR, met the mNY criteria, not significantly different from the HLA-B27(+) proportion observed among axSpA probands who did not have an affected FDR (210/263 (79.8%), p=0.20; OR=1.87, 95% CI (0.70 to 4.98)). Coexistence of both types of the disease (radiographic and non-radiographic) occurred in about 10% of the families.

AAU associated with axSpA

Symptoms suggestive of AAU (one or more episodes of unilateral painful inflamed red eye, and prescription of eye drops containing steroids) occurred significantly more often among FDR who during follow-up developed axSpA than among those who did not: 13/34 (38.2%) vs 29/251 (11.6%), p=0.00004; OR=4.74, 95% CI (2.15 to 10.47). Comparing only HLA-B27(+) FDR, 13/34 (38.2%) HLA-B27(+) FDR who developed axSpA had symptoms suggestive of AAU in contrast to 14/114 (12.3%) HLA-B27(+) FDR without axSpA (p=0.0006, OR=4.42, 95% CI (1.82 to 10.76)). The prevalence of AAU symptoms among FDR with axSpA (38.2%) is similar to the prevalence of AAU among HLA-B27(+) probands: 35/79 (44.3%) for HLA-B27(+) probands, p=0.55). The low prevalence (12.3%) of AAU symptoms in HLA-B27(+) FDR without axSpA does not differ significantly from the 10.9% (15/137) figure for healthy HLA-B27(-) FDR (p=0.74).

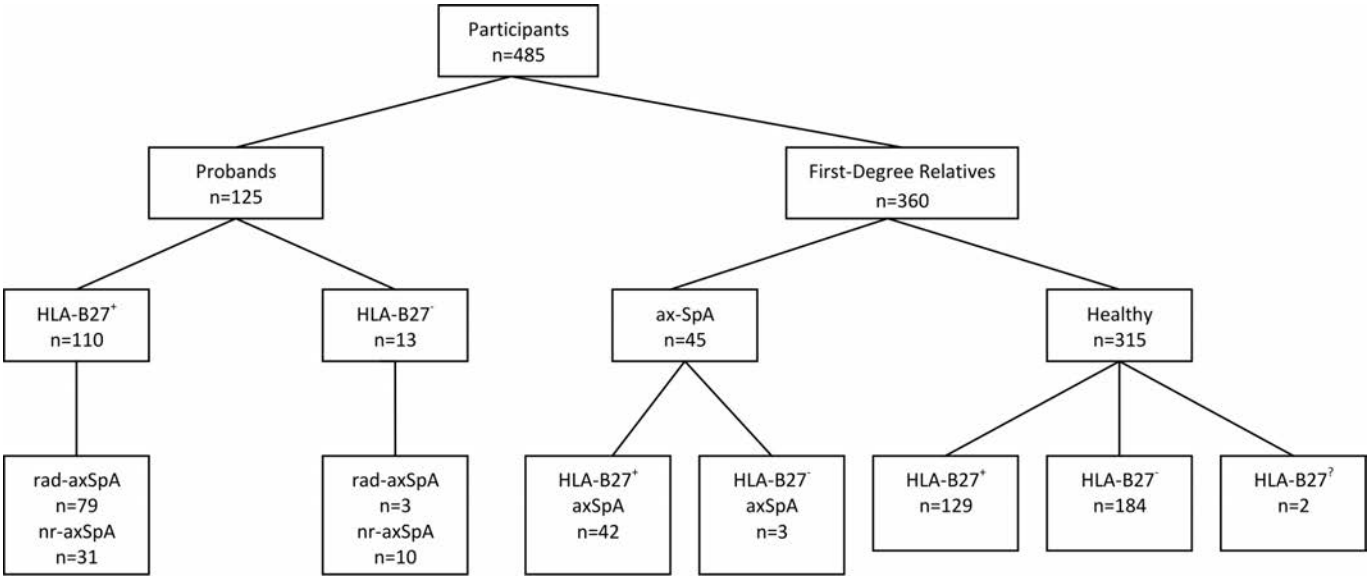

Figure 1 Flow chart of probands with axial spondyloarthritis (axSpA) by HLA-B27 and radiographic status. First-degree relatives are classified as axSpA or healthy and HLA-B27 status. axSpA, axial spondyloarthritis; HLA-B27+, HLA-B27 positive; HLA-B27-, HLA-B27 negative; HLA-B27?, HLA-B27 unknown; nr, -axSpA, non-radiographic axSpA.

Back pain as a predictor for axSpA

At baseline (1985) CIBP[14] was reported significantly more often (46/286, or 16.1%) by HLA-B27(+) FDR without radiographic sacroiliitis (mean age ±SD 28.3±8.1 year) than by 27/272 (9.9%) healthy HLA-B27(-) FDR (mean age ±SD 28.4±7.4 year) (OR=1.74, p=0.031). Nonetheless, the onset of CIBP at early age was not a reliable predictor of axSpA. Of the 35 HLA-B27(+) new cases of axSpA who developed the disease between 1986 and 2019 and who had normal SI joints in 1985, 31 had complete data for CIBP at baseline and follow-up. CIBP at baseline occurred in 5/31 (16.1%), not very different from the prevalence of CIBP in 1985 among healthy HLA-B27(+) FDR who never developed the disease (18/126, 14.3%) (OR=1.15, p=0.8). Thus, for FDR of AS probands, the presence of CIBP at young age (mean 28 years) does not reliably predict the long-term development of axSpA.

Sensitivity and specificity of clinical features

The clinical history serves as a useful tool in discriminating people with and without axSpA. Items with sensitivity or specificity above 70% for the presence of axSpA are provided in table 2. It shows that, overall sensitivity decreases as specificity increases, and vice versa. Sensitivity was assessed among all AS probands who met the mNY criteria, whereas specificity was appraised in the group of HLA-B27(-) FDR as they are at very low risk of developing the disease. The best performing items cover three anatomical regions: lumbar spine and gluteal region, thoracic spine, and frontal (anterior) chest wall. These three regions contribute diagnostically about equally (table 2).

The diagnostic yield, in particular specificity, could meaningfully be improved by combining the three anatomical regions into one index of three questions: (1) CIBP; (2) complaints at the thoracic region and (3) complaints at the frontal chest wall. Each of three drawings in the questionnaire pointed to the specific location. Two or three of these questions were answered 'yes' by 69/83 AS probands, providing a sensitivity of 83.1% (figure 2). The specificity among the healthy HLA-B27(-) FDR was 116/133 (87.2%) (OR 33.69, 95% CI 15.6 to 72.5) (p<0.00001).

In the whole group of 45 FDR who had been diagnosed as having axSpA at some point in time between 1985 and 2019, 21/44 (47.7%) FDR fulfilled criteria for CIBP; 28/40 (70.0%) reported thoracic complaints; 21/42 (50%) had complaints at the frontal chest wall. The proportion reporting positive answers to ≥2 questions of the three-item composite index among these 'new' axSpA patients was 61.0% (25/41). The specificity of this composite index is 86.3% (101/117) among the HLA-B27(+) healthy FDR.

AxSpA symptoms in 'healthy' relatives

For this analysis, we define 'healthy' to mean never having been diagnosed as suffering from axSpA. Feelings of pain, stiffness or discomfort at the frontal chest wall, the lumbar or thoracic spine occurred in up to 25% of 'healthy' HLA-B27(+) FDR, significantly more than in the HLA-B27(-) healthy relatives (who reported such features in less than 9%) (table 3). These symptoms suggest an inflammatory component for their discomfort. These symptoms tend to cluster in individuals in one anatomical region; in particular complaints at the thoracic spine (last 4 items of table 3) occurred in 9/117 (7.7%) 'healthy' HLA-B27(+) FDR vs only 2/138 (1.4%) of HLA-B27(-) FDR (p=0.015). This suggests possible 'hidden' (undiagnosed) axSpA clinical features, mainly at the thoracic spine and mostly without the well-known CIBP, among genetically predisposed relatives.

DISCUSSION

AS occurs commonly among FDR of HLA-B27(+) probands when they share this susceptibility allele. In this family study spanning 35 years, we observed that ~25% of HLA-B27(+) FDR developed axSpA irrespective of their proband's radiographic status (ie, presence or absence of sacroiliitis), but very rarely among the HLA-B27(-) FDR (3% in this study). Moreover, we observed that AS and nr-axSpA may run in one and the same family. This supports the view of genetic homogeneous propensity of both expressions (radiographic and non-radiographic forms) of the disease, at least where the family involved carries HLA-B27. It illustrates a major role of the family history and

Table 2 Features of clinical history discriminating between AS probands meeting modified New York criteria (sensitivity) and healthy HLA-B27 negative relatives (specificity)

Question	AS Probands Sensitivity no/total (%)		HLA-B27 negative Relatives Specificity no/total (%)		OR (95% CI)	P value
Lumbar Spine region Chronic inflammatory low backpain (Calin)	64/87	73.6	117/138	84.8	15.50 (7.97 to 30.16)	<0.00001
Insidious onset of back pain	72/86	83.7	80/138	58.0	7.09 (3.65 to 13.79)	<0.00001
More than 3 months duration	67/86	77.9	103/138	74.6	10.38 (5.48 to 19.63)	<0.00001
Associated with morning stiffness >30 min	66/86	76.7	102/138	73.9	9.35 (4.99 to 17.52)	<0.00001
Back pain starting before age 40	84/86	97.7	88/138	63.8	73.92 (17.43 to 33.45)	<0.00001
Pain and stiffness	68/87	78.2	105/138	76.1	11.39 (5.99 to 21.63)	<0.00001
Worsening at early morning	56/86	65.1	125/137	91.2	19.44 (9.28 to 40.75)	<0.00001
Waking up during the night because of complaints	56/86	65.1	122/138	88.4	14.23 (7.18 to 28.22)	<0.00001
Leaving bed and walking around during the night	50/84	59.5	131/136	96.3	38.53 (14.26 to 104.08)	<0.00001
Pain irradiating into gluteal region	64/82	78.0	91/138	65.9	6.88 (3.66 to 12.93)	<0.00001
Usage of analgesics	82/86	95.3	86/138	62.3	33.90 (11.73 to 97.96)	<0.00001
Relief of symptoms due to analgesics	73/88	83.0	88/137	64.2	8.74 (4.53 to 16.85)	<0.00001
Thoracic region						
Complaints at thoracic region *ever*	67/84	79.8	106/134	79.1	14.92 (7.59 to 29.33)	<0.00001
Pain and stiffness	47/88	53.4	131/138	94.9	21.45 (9.01 to 51.11)	<0.00001
Complaints at early morning	54/86	62.8	116/138	84.1	8.90 (4.73 to 16.73)	<0.00001
Morning stiffness at thoracic spine region	45/84	53.6	132/137	96.4	30.46 (11.31 to 82.03)	<0.00001
Complaints if body position does not change	52/83	62.7	119/137	86.9	11.09 (5.70 to 21.58)	<0.00001
Usage of analgesics	48/85	56.5	129/137	94.2	20.92 (9.09 to 48.12)	<0.00001
Relief of symptoms due to analgesics	46/87	52.9	130/138	94.2	18.23 (7.96 to 41.76)	<0.00001
Ventral chest wall region						
Complaints at ventral chest wall region ever	62/86	72.1	113/136	83.1	12.69 (6.62 to 24.32)	<0.00001

Included items are presented by anatomical region and have sensitivity and/or specificity >70%.
AS, ankylosing spondylitis.

putative additional familial factors as predictor of development of axSpA.[5 15 16]

One might wonder whether the cumulative axSpA incidence of ~25% for HLA-B27(+) FDR might be inflated by *selection bi*as or case-ascertainment (clinical examination at baseline and patient reported information at follow-up).

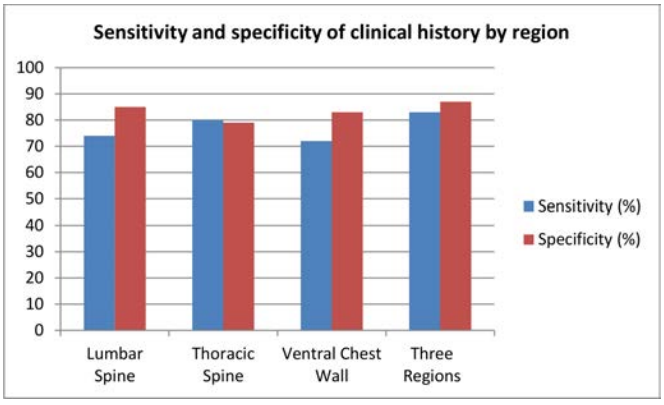

Figure 2 The clinical history can be used as a diagnostic tool. Sensitivity and specificity of complaints at three anatomical regions are provided for each region separately and for a composite index of complaints at these three regions (right). Complaints of the lumbar spine were assessed by chronic inflammatory back pain (positive if ≥4 (of 5) Calin items are met). The thoracic spine was evaluated by complaints of pain and discomfort at the dorsal spine. Pain and discomfort at the ventral chest wall were likewise appraised. The three region index was considered positive if complaints at ≥2 regions were present.

Selection bias would have occurred if symptomatic HLA-B27(+) FDR who had developed axSpA after baseline would have preferentially volunteered to participate in the follow-up study. In fact, the proportion participating HLA-B27(+) FDR was even slightly lower compared with baseline: in 1985 360/668 (53.9%) FDR of HLA-B27(+) probands were HLA-B27(+) compared with 162/329 (49.2%) at follow-up.

Ascertainment of diagnosis at baseline (clinical diagnosis at the study centre) differed from ascertainment at follow-up (patient reported diagnosis by a Swiss rheumatologist). Moreover, the concept of disease has broaden in the last two decades. This may have impacted (inflated) our axSpA incidence ~25% figure. However, as our findings illustrate, 'AS without sacroiliitis' was already known in 1985,[8] and the Rome criteria[17] allow the diagnosis if 4 of 5 clinical criteria are met in the absence of definite sacroiliitis. In recent decades the broader concept of axSpA has become widely accepted. The increased awareness and improved imaging (MRI) have promoted better recognition of axSpA. Taking the differences in case-ascertainment into account, a somewhat higher prevalence figure than the earlier reported 21% figure[5] seems sensible.

The occurrence at baseline of 'AS without radiographic sacroiliitis' among axSpA probands, shown in table 1, illustrates that this entity is nowadays widely known as nr-axSpA.

Uveitis as a predictor for axSpA

AAU is a common, usually unilateral, HLA-B27 associated, intraocular inflammatory disease, concomitantly occurring in patients with axSpA. The prevalence of AAU in AS increases with disease duration, and may exceed 50%, particularly in HLA-B27(+) patients with longstanding disease.[18–23] We accepted

Table 3 Prevalence of symptoms suggesting 'hidden' axial SpA among HLA-B27 positive FDR compared with HLA-B27 negative FDR

Question	Relatives HLA-B27 positive no positive/total and percentage		Relatives HLA-B27 negative no positive/total and percentage		OR	95% CI	P value
Change of body position causes exacerbation of complaints at the ventral chest wall	6/114	5.3	1/138	0.7	7.61	0.90 to 64.18	0.029
Worsening of low back pain during the early morning before getting up	28/111	25.2	12/137	8.8	3.51	1.69 to 7.30	0.00046
Persisting low back pain after getting up	19/117	16.2	11/137	8.0	2.22	1.01 to 4.88	0.043
Waking up regularly after 14:00 hour because of pain or discomfort at the thoracic spine	7/116	6.0	1/137	0.7	8.73	1.06 to 72.07	0.016
Morning stiffness at the thoracic spinal region	11/117	9.4	5/137	3.6	2.74	0.92 to 8.13	0.06
Morning stiffness at the thoracic spinal region for at least 15 to 60 min	8/117	6.8	2/138	1.4	4.99	1.04 to 23.99	0.027
Improvement of stiffness at the thoracic spinal region through exercises	12/112	10.7	5/134	3.7	3.10	1.06 to 9.08	0.032
Exercising improves thoracic complaints due to sustained body position	17/116	14.7	9/136	6.6	2.42	1.04 to 5.67	0.037

None of these FDR of HLA-B27 positive axSpA probands had ever been diagnosed as axSpA.
axSpA, axial spondyloarthritis; FDR, first-degree relatives.

participants' reply of having used corticosteroid containing eye drops as the most important proxy for a diagnosis of AAU. Although this might have face validity, it is not a firm proof. With this limitation in mind, AAU was significantly associated with development of axSpA, whereas there was no difference in occurrence of AAU between healthy HLA-B27(+) and HLA-B27(-) FDR. This is compatible with the reported 45% association of HLA-B27 with AAU in the general population, that is, about equally in HLA-B27(+) and HLA-B27(-) individuals.[24]

The stronger association of AAU with axSpA than with HLA-B27 might, at least partly, be due to diagnostic suspicion bias, that is, an established diagnosis (say axSpA) might increase the likelihood that an associated disease (say AAU) will be diagnosed appropriately. Nonetheless, our findings are strongly supported by recent genome-wide association studies revealing that the association of AAU and axSpA is primarily with the full genetic overlap (HLA and non-MHC genes) of both conditions rather than with the HLA-B27 allele alone.[15 23] One may conclude that AAU is more closely related to the rheumatologic disease than to the HLA-B27 allele, and therefore, may predict future axSpA. Literature indicates that among HLA-B27(+) AAU patients the prevalence of concomitant axSpA may rise to about 80%, illustrating that occurrence of AAU among relatives warrants screening for axSpA.[19]

Chronic back pain as a predictor for axSpA

CIBP at young age failed to predict future development of axSpA in our study. Reveille *et al*[25] reported that FDR of AS patients had earlier onset of CIBP than those with non-IBP, and that their CIBP persisted longer (73% of the FDR still had CIBP after a mean of 5.5 years). On the other hand, Wang *et al*[26] found that a minority of patients with new onset IBP progressed to SpA, while IBP resolved in many. They suggest that the finding that IBP often reso lves may explain the difference between the prevalence of IBP (3%–6%) and the prevalence of SpA (0.4%–1.3%). Of note, at baseline 16.1% (46/268) of our HLA-B27(+) FDR had CIBP without sacroiliitis vs 9.9% (27/272) of the HLA-B27(-) FDR (p=0.03), but there was no difference observed at follow-up 35 years later. This supports the view that CIBP might be a potentially resolving manifestation of axSpA, that is, a favorable outcome of the disease. This view is also supported by recently published findings from the pre-SpA cohort study. IBP was reported by 19% of seemingly healthy FDR (of HLA-B27(+) axSpA patients) with an equal distribution between HLA-B27(+) and HLA-B27(-) FDR. Progression from subclinical inflammation to clinical axSpA within 1 year of follow-up occurred in 6%, and was mainly (86%) observed in HLA-B27(+) FDR.[20]

Clinical history as an aid to diagnosis

For axSpA the diagnostic yield and accuracy might improve by paying close attention not only to the well-known inflammatory symptoms at the lumbar spine,[14 27] but also to complaints of pain and discomfort at the thoracic spinal and the frontal chest wall region. Combining features at these three anatomical regions into a *triad* yielded high (87%) specificity. While our study requires independent validation, this finding compares quite well with Rudwaleit's refined set of criteria for CIBP that have a sensitivity of 70.3% and specificity of 81.2% if at least two of the four parameters (morning stiffness of >30 min' duration, age at onset of back pain, no improvement in back pain with rest, awakening because of back pain during the second half of the night only, alternating buttock pain and time period of the onset of back pain) were fulfilled.[27] It would be worthwhile to combine and evaluate the refined CIBP criteria with complaints of pain and discomfort at the thoracic spine and the chest wall. If such studies would also demonstrate high specificity and sufficient sensitivity, then the composite triad index of complaints of pain and discomfort at lumbar spine, thoracic spine and chest wall might also provide the needed improvement of the specificity of the current classification criteria for axSpA that is being addressed in the ongoing CLASSIC study.[28 29]

In summary, about 25% of FDR of HLA-B27(+) probands with axSpA also develop the disease. Occurrence of AAU among FDR of patients with axSpA calls for screening for the disease, but presence of CIBP among young FDR has no long-term predictive value for the diagnosis axSpA. Paying attention to prevailing symptoms of pain and discomfort at the thoracic spine and the frontal chest wall in addition to CIBP may improve the diagnostic yield and classification of axSpA. 'Healthy' HLA-B27(+) FDR with such symptoms may have unnoticed 'hidden' axSpA, that may not be captured by the current sets of criteria or fall short of being diagnosed properly.

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Contributors All authors had full access to all of the data in the study and take responsibility for the data and the accuracy of the data analysis. Concept and design: SMvdL, MAK, HB, HvZ and MAB conceived the study. SMvdL, HB and HvZ designed the questionnaire. Drafting of the manuscript: SMvdL, MAK and MAB. Genetical analysis: ZL and MAB. Statistical analysis: SMvdL, ZL, KK and MAB. Obtained funding: SMvdL and MAB. Administrative, technical or material support: HvZ and PMV. Acquisition of data: SMvdL, HvZ and PMV. Critical revision of the manuscript for important intellectual content: all authors. Guarantor: SMvdL.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ethical Committee of the Swiss Kanton Bern (2017-00536). Participants gave informed consent to participate in the study before taking part.

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CLINICAL SCIENCE

Tocilizumab in patients with new onset polymyalgia rheumatica (PMR-SPARE): a phase 2/3 randomised controlled trial

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ABSTRACT

Background Polymyalgia rheumatica is the second most common inflammatory rheumatic disease of people >50 years. Glucocorticoid therapy is highly effective, but many patients require treatment for several years. Effective glucocorticoid sparing agents are still needed.

Methods In this double-blind, multi-centre phase 2/3 clinical trial, we randomly assigned 36 patients with new onset polymyalgia rheumatica from three centres to receive subcutaneous tocilizumab (162 mg per week) or placebo for 16 weeks (1:1 ratio). All patients received oral prednisone, tapered from 20 mg to 0 mg over 11 weeks.

The primary endpoint was the proportion of patients in glucocorticoid-free remission at week 16; key secondary endpoints, including time to first relapse and cumulative glucocorticoid dose at weeks 16 and 24, were evaluated.

Results From 20 November 2017 to 28 October 2019 39 patients were screened for eligibility; 19 patients received tocilizumab and 17 placebo. Glucocorticoid-free remission at week 16 was achieved in 12 out of 19 patients on tocilizumab (63.2%) and 2 out of 17 patients receiving placebo (11.8%, p=0.002), corresponding to an OR of 12.9 (95 % CI: 2.2 to 73.6) in favour of tocilizumab. Mean (±SD) time to first relapse was 130±13 and 82±11 days (p=0.007), respectively, and the median (IQR) cumulative glucocorticoid dose was 727 (721–842) mg and 935 (861–1244) mg (p=0.003), respectively. Serious adverse events were observed in five placebo patients and one tocilizumab patient.

Conclusion In patients with new onset polymyalgia rheumatica undergoing rapid glucocorticoid tapering, tocilizumab was superior to placebo regarding sustained glucocorticoid-free remission, time to relapse and cumulative glucocorticoid dose.

Trial registration number NCT03263715

Key messages

What is already known about this subject?

⇒ Treatment of polymyalgia rheumatica is primarily based on glucocorticoids, which are recommended for at least 12 months, but may extend to several years, in some cases even being life-long, leading to glucocorticoid-related adverse events in up to 65% of the cases.

⇒ Small and uncontrolled studies investigating tocilizumab, an inhibitor of the interleukin-6 receptor, were indicative of its high clinical potential, but randomised controlled trials testing the clinical efficacy of tocilizumab are not available.

What does this study add?

⇒ The results from this PMR-SPARE trial show a high clinical efficacy of tocilizumab compared with placebo for the treatment of new onset polymyalgia rheumatica.

⇒ The evidence provided adds a major therapeutic option to a disease where to date no therapies are approved for sparing glucocorticoids.

How might this impact on clinical practice or future developments?

⇒ The results of this trial provide scientific evidence of superiority of tocilizumab compared with placebo for treatment of polymyalgia rheumatica.

⇒ The data provided may serve as basis for future approval of tocilizumab for the indication of polymyalgia rheumatica and facilitate its reimbursement in this patient group.

INTRODUCTION

Polymyalgia rheumatica is the second most common inflammatory rheumatic disease in the elderly after rheumatoid arthritis, with a peak incidence around 70 years of age.[1] It is clinically characterised by neck, bilateral shoulder and hip girdle pain as well as by morning stiffness which severely impairs patients' daily activities.[2] Polymyalgia rheumatica is thought to be caused by a systemic inflammatory response that is mainly driven by interleukin(IL)-6. Inflammatory markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are almost invariably markedly elevated in these patients.[3]

Treatment of polymyalgia rheumatica is primarily based on glucocorticoids at intermediate doses, which are recommended for at least 12 months.[4] Treatment duration with glucocorticoids in clinical practice, however, is often much longer and may even be life-long.[5 6] There is usually a rapid initial response to glucocorticoids, but relapses occur in 50% of patients during tapering.[7] Long-term use of glucocorticoids is associated with adverse

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events in up to 65% of patients, including infections, diabetes, hypertension, weight gain, cataracts, glaucoma, osteoporosis and skin changes.[8] Few glucocorticoid sparing agents have been investigated in polymyalgia rheumatica yet with mixed results. Most evidence from randomised controlled trials is available for methotrexate; however, its effect in reducing cumulative glucocorticoid doses and preventing relapses is only moderate at best.[9] Inhibitors of tumour necrosis factor α were ineffective in trials,[10 11] and azathioprine revealed only a small benefit on the daily glucocorticoid dose after 12 months.[12] Given the high risk of adverse events resulting from long-term use of glucocorticoids in clinical practice,[13] effective glucocorticoid sparing agents are a major unmet need in the management of polymyalgia rheumatica.[14]

Given the profoundly elevated levels of IL-6 and the acute phase reactants induced by this proinflammatory cytokine,[15 16] inhibition of the IL-6 pathway constitutes an attractive therapeutic approach for polymyalgia rheumatica. Several case reports, case series and open label clinical studies suggested an excellent clinical effect of tocilizumab. While these studies delivered a clear proof of concept, most concluded that randomised controlled trials of IL-6 inhibition in polymyalgia rheumatica are warranted.[17–20] We conducted a double blind, randomised, placebo-controlled clinical trial to investigate the efficacy and safety of tocilizumab compared with placebo in patients with new onset polymyalgia rheumatica receiving background glucocorticoid therapy.

METHODS

Study design and patients

This is a 24-week randomised, double-blind, placebo-controlled, phase 2/3 trial, the polymyalgia rheumatica glucocorticoid sparing (PMR-SPARE) trial, to investigate whether treatment with tocilizumab resulted in higher rates of glucocorticoid-free remission at week 16 compared with placebo, in patients with new onset polymyalgia rheumatica. All patients received a rapid glucocorticoid tapering protocol that allowed confining glucocorticoid exposure to 11 weeks unless a relapse occurred. Safety and efficacy aspects were monitored for 24 weeks (online supplemental table 1). The trial protocol, including the statistical analysis plan, is available in the online supplemental appendix 2. The study is registered at ClinicalTrials.gov.

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided their written informed consent. The study was conducted at three centres across Austria (Medical University of Vienna, Medical University of Graz and Hietzing Hospital Vienna). A web-based randomisation algorithm provided by the Medical University of Vienna was used as described in the study protocol. Blinding and treatment allocation was performed by an unblinded study team of the Medical University of Vienna, data base maintenance and monitoring was performed by the Coordination Centre for Clinical Studies (KKS) of the Medical University of Vienna. These investigators were not involved in any other part of the study.

Patients enrolled fulfilled the provisional 2012 European League Against Rheumatism – American College of Rheumatology classification criteria for polymyalgia rheumatica at screening and baseline.[21] A clinical diagnosis of polymyalgia rheumatica could have been established up to 2 weeks before the screening visit, during which period a maximum amount of glucocorticoids at 25 mg prednisone equivalent per day was allowed. Patients with evidence of other inflammatory rheumatic diseases or other conditions requiring systemic treatment with glucocorticoids were excluded. Patients with giant cell arteritis (cranial or large vessel) as indicated by unequivocal clinical symptoms, imaging or biopsy results were excluded; however, screening by imaging or biopsy was not mandated as this currently does not reflect clinical practice.[7]

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.

Randomisation and masking

Patients were randomly assigned to one of two groups in a 1:1 ratio. One specific aspect in PMR-SPARE was the blinding towards acute phase reactants, since inhibition of the IL-6 receptor by tocilizumab would strongly impact CRP and ESR levels and therefore could indirectly unblind treatment allocation. This could also increase the risk of incorrect rejection of the null hypothesis on the primary outcome of glucocorticoid-free remission if acute phase reactants were part of this assessment. The investigators and clinical assessors in the trial were therefore not only blinded to the treatment allocation, but also to the results of CRP and ESR, as well as to other laboratory markers that may have unblinded the group allocation, such as fasting lipids and liver enzymes. A dedicated laboratory assessor in each study centre, who was also blinded to the treatment allocation but not involved in any other parts of the study, reviewed the laboratory results. The results were not disclosed to any other investigator.

Procedures

The 'tocilizumab' group received tocilizumab 162 mg as subcutaneous injection every week; the 'placebo' group received matching placebo injections every week. The 24-week double-blind period consisted of a 16-week treatment phase followed by an 8 week follow-up for the assessment of safety and maintenance of response. All patients received oral glucocorticoids in conjunction with a rapid tapering scheme starting with 20 mg prednisone at baseline (irrespective of the pre-baseline dose), tapering the daily dose by 2.5 mg every week until a dose of 10 mg has been used for a week; subsequently the daily prednisone dose was reduced to 9 mg (week 6), 7 mg (week 7), 5 mg (week 8), 4 mg (week 9), 2 mg (week 10) and 1 mg (week 11); after week 11, no glucocorticoids were applied per regular scheme. The protocol also included a prespecified treatment regimen for relapse, according to which the prednisone dose was increased by 5 mg for 1 week. If clinical remission was re-achieved, the prednisone dose was tapered at the discretion of the investigator within 4 weeks to the pre-relapse dose; if remission was not achieved, then the prednisone dose was further increased and subsequently tapered at the discretion of the investigator until the pre-relapse dose was reached. Thereafter, the pre-specified tapering protocol was followed again.

Outcomes

The primary efficacy endpoint was the achievement of glucocorticoid-free remission at week 16. Key secondary efficacy endpoints were glucocorticoid-free remission at weeks 12 and 24, time to first relapse and cumulative prednisone doses at weeks 16 and 24. Safety was documented and evaluated for incidence and severity of adverse events in all patients who had received at least one dose of tocilizumab or placebo.

At every visit after baseline, patients were assessed for the presence of remission, which was defined as the absence of stiffness at shoulder and/or hip girdle attributable to active polymyalgia rheumatica, as judged by a blinded investigator. Pain and stiffness are part of the OMERACT core domain set for polymyalgia rheumatica.[22] Relapse was defined in accordance with previous studies[10 23] as recurrence of signs of active polymyalgia rheumatica, that is, the return of aching and stiffness at shoulders, hip girdle or both, as adjudicated by the blinded investigator. At every visit, an additional blinded efficacy assessor obtained patient and assessor global scores, patient pain score, morning stiffness (all on 100 mm Visual Analogue Scales (VAS)) and evaluated physical function by the 'elevation of the upper limb score' (semiquantitative scale),[24] the Health Assessment Questionnaire Disability Index (HAQ) and the Short Form-36 (SF-36). Inflammatory markers, CRP and ESR, on which tocilizumab has rapid effects, were determined at each study visit, but were not part of remission/relapse definitions by the investigators, who were blinded to these results to maintain overall blinding. Blinding was further ensured through provision of tocilizumab and placebo in prefilled syringes with matching presentation for the 16 weeks of active therapy. Blinding was maintained throughout the study period.

Statistical analysis

Based on the nature of the disease and the usual need of a slow tapering of glucocorticoids to prevent relapses, we estimated that only 20% of enrolled patients receiving placebo would be able to achieve glucocorticoid-free remission at week 16. In contrast, previous open-label phase 2 trials and proof-of-concept studies suggested a high level of disease control for patients treated with tocilizumab,[17–20] guiding an expected 80% of patients to be in glucocorticoid-free remission at week 16 when treated with tocilizumab. Based on these estimates and a 1:1 sampling ratio, we calculated that a total of 24 patients (12 in the tocilizumab group and 12 in the placebo group) were needed to design a randomised controlled phase 2/3 clinical trial, which would provide 80% power at a significance level of $p<0.05$ using Fisher's exact test on the primary outcome (rate of glucocorticoid-free remission at week 16). We conservatively estimated 30% of patients as potential drop outs/lost to follow-up, and increased the sample size accordingly despite the planned non-responder imputation approach, by which all patients who started treatment would be included in the analysis. The targeted recruitment was therefore 32 patients.

The primary and key secondary endpoints were tested between the groups using either Fisher's exact tests for categorical variables, Kruskal-Wallis tests for non-normally distributed continuous data or Kaplan-Meier estimator for time-to-event data. To control for type I error of the secondary endpoints, we applied a strategy of hierarchical testing, by which hypothesis testing continues until reaching the first non-significance. The pre-determined hierarchy for testing secondary endpoints was: proportion of subjects in glucocorticoid-free remission at week 12 → proportion of subjects in glucocorticoid-free remission at week 24 → time to first relapse → cumulative dose of prednisone at week 16 → cumulative dose of prednisone at week 24 → proportion of subjects with increased ESR >20 mm/hour, or increased CRP levels >5 mg/L at week 24 → patient pain (VAS) at week 16 → patient global assessment of disease activity (VAS) at week 16 → evaluator global assessment (VAS) at week 16 → SF-36 at week 16 → HAQ at week 16. Other secondary outcomes as stated in the protocol, including safety assessment, were considered exploratory.

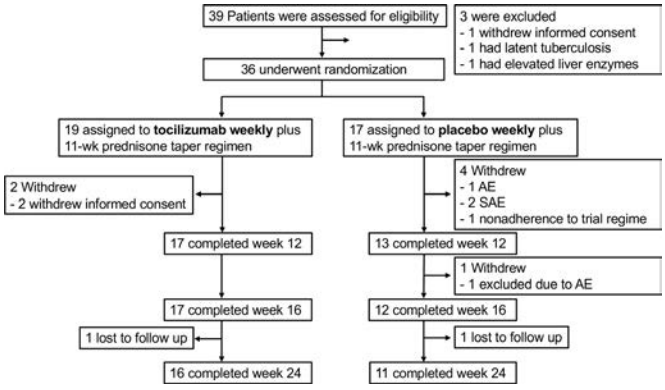

Figure 1 Screening, randomisation and follow-up of patients at week 16 (primary endpoint) and week 12/24 (secondary endpoints). AE, adverse event; SAE, serious AE.

Analyses were based on an intent-to-treat approach using non-responder imputation for binominal endpoints, and the last observation carried forward method for continuous endpoints, for all visits after patients have dropped out of the study or were lost to follow- up. In the Kaplan-Meier analysis, all patients were included in the estimate of time-to-relapse, censoring patients without event (ie, without relapse) or those lost to follow-up. The statistical analysis plan was registered and submitted as part of the study protocol before study initiation and was not amended thereafter. Statistical analysis was performed by HR and AK.

RESULTS

Patients

From 20 November 2017 to 28 October 2019, 39 participants were screened. First baseline visit was on 27 November 2017. The last visit (week 24) was on 2 June 2020.

Of 39 screened patients three patients were excluded and 36 were enrolled, of whom 19 were randomly assigned to receive tocilizumab and 17 to receive placebo; 84% of patients in the tocilizumab group and 65% in the placebo group completed the trial through week 24 (figure 1). Patient characteristics at baseline were not statistically significantly different between the groups (table 1).

Primary and secondary outcomes

A total of 63.2% (12/19) in the tocilizumab group and 11.8% (2/17) in the placebo group achieved glucocorticoid-free remission at week 16 ($p=0.002$, figure 2A); this state was maintained after withdrawal of tocilizumab at week 16 in 91.7% (11/12) of patients over additional 8 weeks of blinded follow-up until week 24. With respect to achieving the primary endpoint (at week 16), these numbers correspond to an OR of 12.9 (95% CI: 2.2 to 73.6) in favour of tocilizumab.

Hierarchical testing of secondary endpoints revealed statistical significance in favour of tocilizumab versus placebo for glucocorticoid-free remission at weeks 12 and 24 ($p=0.02$ for both, figure 2A); time to first relapse ($p=0.007$); and cumulative prednisone dose at week 16 ($p=0.003$) and week 24 ($p=0.001$) (table 2; online supplemental figure 1). Using time-to-event analysis (Kaplan-Meier estimator) time to first relapse was also in favour of tocilizumab (log-rank test $p=0.007$, figure 2B). The estimated mean time to first relapse was 130 days (±13) in the tocilizumab group and 82 days (±11) in the placebo group.

The median cumulative prednisone dose over 16 weeks amounted to 727 mg (IQR 721–842) in the tocilizumab group

Table 1 Demographic and disease characteristics of patients at baseline*

Characteristic	Tocilizumab N=19	Placebo N=17
Age (years)	68.8±9.0	71.1±9.0
Female sex	52.6%	52.9%
Caucasian ethnicity	100%	100%
Weight (kg)	81.7±28.5	72.0±13.9
Body mass index (kg/m^2)	26.5±4.5	25.7±3.9
Disease duration (days) at screening	8±5	6±3
Patients on prednisone	100%	94%
Current prednisone dose (mg)	16.7±3.9	17.2±3.1
Erythrocyte sedimentation rate (mm/hour)	24.3±16.4	24.1±18.7
C-reactive protein (mg/dL)	1.6±2.4	0.98±1.5
Pain by Visual Analogue Scale (mm)	30.8±26.0	22.8±16.7
Patient global assessment of disease activity by Visual Analogue Scale (mm)	30.1±25.9	26.0±24.4
Heath Assessment Questionnaire (0–3)	0.64±0.60	0.65±0.61
Short Form-36 physical component score (0–100)	47.7±7.5	45.9±5.2

*Data shown are means±SD, unless stated otherwise.

and 935 mg (IQR 861–1244) in the placebo group (p=0.003); over 24 weeks it was 781 mg (IQR 721–972) and 1290 mg (IQR 1106–1809), respectively (p=0.001; online supplemental figure 1). In figure 2C, the mean doses are shown which are more sensitive to depict dose increases of individual patients over time (no statistical analysis done). No significant difference was observed for proportions of patients with increased CRP or ESR at week 24 (table 2), all subsequent outcomes were not formally tested statistically. However, exploratory statistical analysis on secondary outcomes revealed no difference between the two groups (online supplemental table 2). At week 24, median CRP levels in the tocilizumab and placebo groups were 0.28 (IQR 0.09–1.07) and 0.71 (IQR 0.30–2.01) mg/dL, respectively (p=0.15); and median ESR levels were 12 (IQR 11–35) and 12 (IQR 6–20) mm/hour (p=0.12; online supplemental table 3).

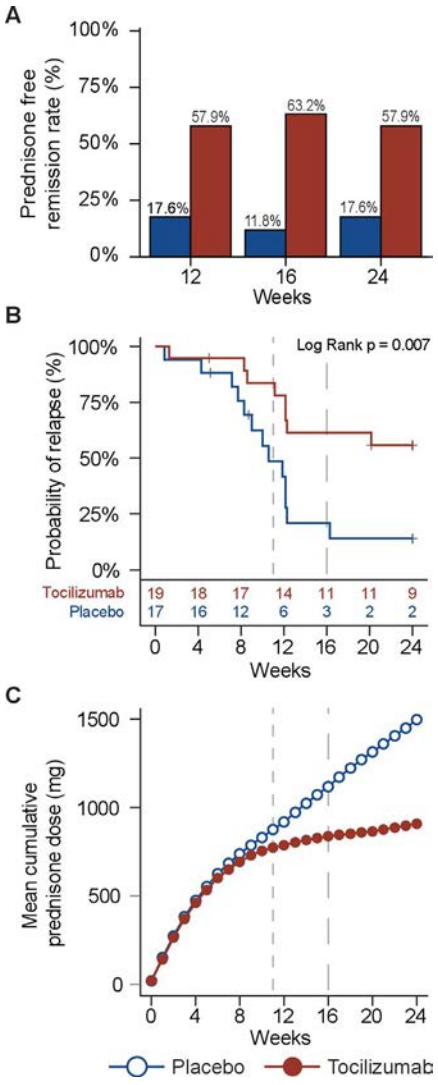

Figure 2 **Efficacy analysis for patients treated with tocilizumab or placebo.** (A) Glucocorticoid-free remission at weeks 12, 16 (primary endpoint; p=0.002) and 24. (B) Time to relapse (Kaplan-Meier curves censoring patients who dropped out or were lost to follow-up). (C) Mean cumulative prednisone dose over time.

Safety

The total number of adverse events per 100 patient-years was 490.6 (468.9–523.2) in the tocilizumab group and 555.0 (531.9–579.0) in the placebo group (table 3). In 41% of patients in the placebo group, clinical musculoskeletal adverse events were recorded, which had not been adjudicated as flare by the respective investigators. The most frequent adverse events were infections, which occurred in 63% of patients in the tocilizumab group and 35% in the placebo group, none of them were serious (online supplemental table 4). None of the patient of the tocilizumab or the placebo group held treatment. One patient in the tocilizumab group and five patients in the placebo group developed serious adverse events. None of the patients in the tocilizumab group and two patients in the placebo group withdrew due to serious adverse events: one had pancreatitis and one a duodenal ulcer. In the placebo group, one patient was withdrawn because of a dental abscess and one developed seronegative rheumatoid arthritis. No gastrointestinal perforations, anaphylaxis, myocardial infarctions or malignancies were reported. There were no deaths during the trial period.

Sensitivity analyses

To confirm robustness of the results, we performed two sensitivity analyses: first, we performed a per-protocol evaluation of the primary outcome (instead of the intent-to-treat analysis) to address the impact of the observed imbalance in drop outs between the two study arms on the results: 12/17 (70.6%) patients achieved glucocorticoid-free remission at week 16 in the tocilizumab group and 2/12 (16.7%) in placebo group (p=0.004), the corresponding OR for tocilizumab versus placebo was 13.5 (2.0–90.7). Second, we performed a post-hoc analysis, in which we included information on CRP and ESR in addition to the clinical evaluation of remission, since the study design had required blinding of investigators to these measures, and could therefore not be part of the remission assessment: if normal CRP and ESR would have been required for remission, none of the patients in the placebo group would have achieved glucocorticoid-free remission at week 16, whereas the number of patients in remission remained the same in the tocilizumab group 12/19 (63.2%), where all patients had suppressed CRP/

Table 2 Secondary endpoints in the intention-to-treat population

Testing hierarchy	Secondary endpoints*	Tocilizumab	Placebo	P value
1	Proportion of patients in glucocorticoid-free remission at week 12	57.9%	17.6%	0.02
2	Proportion of patients in glucocorticoid-free remission at week 24	57.9%	17.6%	0.02
3	Time to first relapse (days; mean±SE)	130 (±13)	82 (±11)	0.007
4	Cumulative prednisone dose at week 16 (mg)	727 (721–842)	935 (861–1244)	0.003
5	Cumulative prednisone dose at week 24 (mg)	781 (721–972)	1290 (1106–1809)	0.001
6	Proportion of subjects with increased ESR (>20 mm/hour) at week 24 or Proportion of subjects with increased CRP (>5 mg/L) at week 24	21.1% 42.1%	47.1% 52.9%	n.r. n.r.
7	Pain by Visual Analogue Scale (mm) at week 16	12.0 (4.0–29.0)	15.0 (1.5–45.5)	n.d.
8	Patient global assessment of disease activity by Visual Analogue Scale (mm) at week 16	8.0 (3.0–25.0)	16.0 (3.0–50.0)	n.d.
9	Evaluator global assessment by Visual Analogue Scale (mm) at week 16	2.0 (0–6.0)	5.0 (1.0–30.0)	n.d.
10	Short Form-36 (Physical Component Score) at week 16	56.3 (48.8–61.0)	46.9 (42.2–49.8)	n.d.
11	Health Assessment Questionnaire (0–3) at week 16	0.0 (0.0–0.5)	0.88 (0.13–1.13)	n.d.

n.d., not done; n.r., not reported.
*Data shown are medians and IQRs, unless stated otherwise.
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

ESR by the study drug; vice versa, clinical flares in the tocilizumab treated group were not accompanied by elevated CRP or ESR levels.

DISCUSSION

The PMR-SPARE trial showed that tocilizumab at the standard dose of single weekly injections of 162 mg is superior to placebo in achieving glucocorticoid-free remission at 16 and 24 weeks in patients with new-onset polymyalgia rheumatica subjected to an 11 weeks tapering regime of oral glucocorticoids. Tocilizumab also reduced the occurrence of relapses and reduced the cumulative glucocorticoid dose by almost 40% by week 24.

The observation that glucocorticoid-free remission rates were up to 50% higher in tocilizumab-treated patients compared with those receiving placebo, are in line with results of the Giant-Cell Arteritis Actemra (GiACTA) trial. In that randomised study on tocilizumab in giant cell arteritis about 40% higher rates of remission were observed in tocilizumab as compared with placebo arms,[25] ultimately leading to breakthrough therapy designation for tocilizumab by the US Food and Drug Administration and the European Medicines Agency for giant cell arteritis.

We observed a lower proportion of patients achieving the primary endpoint in the treatment group (63% achieved glucocorticoid-free remission) as compared with previous open-label studies, where responses to tocilizumab were seen in 100%.[19 20] Aside from differences in populations, trial design and outcome measures, this indicates the importance of randomised controlled trials in quantifying and establishing the efficacy of new therapies. Beside a potential additional placebo effect, the rapid tapering of glucocorticoids and the thereby generated lower cumulative glucocorticoid dose may have contributed to the reduced efficacy as compared with previous open-label studies. Post-hoc sample size calculations using the actually observed responses rates in our trial, would have led to 33 patients per group, and therefore would have still been smaller than the recruited number of 36 patients.

The present trial was not designed to compare tocilizumab to glucocorticoids or another drug (eg, methotrexate), nor to test rapid tapering of glucocorticoids against another tapering scheme. Also, PMR-SPARE did not aim to investigate refractory or glucocorticoid resistant disease. Rather, the underlying assumptions were that fast and effective induction therapy with glucocorticoids should not be withheld from patients with polymyalgia rheumatica, and that a shorter course of glucocorticoids is safer than their prolonged use.[26 27] The full clinical effect of tocilizumab was further expected to require several weeks as observed in previous open-label studies with tocilizumab monotherapy.[19] Tocilizumab was superior to placebo not only concerning the primary endpoint, but also regarding all those secondary endpoints, which considered the need for glucocorticoids as treatment failure (ie, proportion of patients in glucocorticoid-free remission, time to first relapse and cumulative glucocorticoid dose). One implicit conclusion from the significantly lower doses of glucocorticoids required in the tocilizumab compared with the placebo-treated patients would be that the risk of glucocorticoid associated adverse effects was also lower,[8 28] however, our study by its design, the low number of patients and the short observational time cannot confirm such assumption.

Table 3 Safety over the 24-week trial period

Variable	Tocilizumab (n=19)	Placebo (n=17)
Duration in trial patient-years	8.2	6.3
Patients with ≥1 adverse event (AE)—no. (%)	16 (84)	14 (82)
No. of events	40	35
Rate per 100 patient-years (95% CI)	490.6 (468.9 to 523.2)	555.0 (531.9 to 579.0)
Patient with AE according to system organ class—no. (%)		
Infection	12 (63)	6 (35)
Musculoskeletal or connective-tissue disorder	0	7 (41)*
Gastrointestinal disorder	3 (16)	4 (24)
Malignancy	0	0
Patients who withdrew from trial because of AE—no. (%)	0	3 (18)
Patients with serious AE—no. (%)	1† (5)	5† (29)
Serious infections	0	0

*Musculoskeletal reports not related to polymyalgia rheumatica disease activity by discretion of investigator.
†One patient in the tocilizumab group had a serious AE (retinal detachment) and five patients in the placebo group developed serious AEs leading to hospital admission (one pancreatitis, one duodenal ulcer, one diarrhoea (not related to an infection), one heat stroke, one suspected giant cell arteritis).

To address this, larger studies would be required, but supportive evidence from comparable populations may be considered as best surrogate. Even the four-arm GiACTA trial trial studying 250 people within four groups was unable to demonstrate a reduction of glucocorticoid associated adverse events despite the impressive glucocorticoid sparing. Data from registries and other studies involving a large number of subjects are required to confirm what we can only speculate from current tocilizumab trials in giant cell arteritis and polymyalgia rheumatica, namely that treatment of these patients with tocilizumab will ultimately reduce the burden from glucocorticoid-related adverse events. Safety in the elderly was also studied in patients with rheumatoid arthritis.[29 30]

Interestingly during the trial musculoskeletal adverse events were reported only in the placebo group. Would one consider all these events were unrecognised flares of polymyalgia rheumatica, then the observed differences between placebo and tocilizumab would be even more pronounced in favour of tocilizumab.

PMR-SPARE did not address the sustainability of tocilizumab treatment beyond 8 weeks after its application. Therefore, it is difficult to conclude whether tocilizumab has disease-modifying properties or might even be curative in some individuals, or if it is simply symptom controlling. The sustained glucocorticoid-free remission over the 8 weeks after their last application of tocilizumab in the trial may indicate that effects of the compound go beyond mere symptom control. In addition no difference was observed at week 24 for CRP and ESR levels between tocilizumab and placebo treated patients, which might be due to higher rates of glucocorticoid use in the latter. Whether drug-free remission could be maintained for longer or symptoms recur in a proportion of patients as in the long-term follow-up of the GiACTA trial trial (~40% flared at 6 months after stopping tocilizumab) is of great interest and has to be clarified by future research. Third, remission and relapse had to be defined purely clinically, as inhibition of the IL-6 receptor was expected to normalise acute phase reactants and may have therefore indirectly unblinded patients' treatment allocation or have biased investigators towards a more frequent adjudication of remission in the tocilizumab group. It is possible that blinding towards ESR and CRP may have increased the uncertainty to define a relapse in both groups, given that activated degenerative shoulder problems may not easily be distinguished from a PMR flare without knowing acute phase reactants.

In summary, the double-blind, randomised, controlled PMR-SPARE study shows the superiority of tocilizumab over placebo, in combination with an 11-week course of glucocorticoids, in achieving glucocorticoid-free remission at week 16, and thus allowing one to spare glucocorticoids in the initial treatment of polymyalgia rheumatica. Effects of tocilizumab were maintained for at least 8 weeks after completion of tocilizumab therapy. Further studies are warranted to evaluate tocilizumab for its long-term sustainment of effects, its optimal duration of therapy, its safety and its use in refractory polymyalgia rheumatica.

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Competing interests AK reports about contracts and personal fees from AbbVie, Bristol Myers Squibb, Celgene, Eli Lilly, Gilead, Merck Sharp and Dohme. RH reports about personal fees from MSD, AbbVie, Pfizer, Lilly, Bristol Myers Squibb, Celgene and Novartis. MB reports about personal fees from Eli Lilly. PM reports speaker fees from AbbVie, Janssen and Novartis and research grants from AbbVie, BMS, Novartis, Janssen, MSD and UCB. MB reports about personal fees from Eli Lilly. DA reports about financial support from Roche to perform this study for the Department of Rheumatology. DA received grants and consulting fees from AbbVie, Amgen, Lilly, Merck, Novartis, Pfizer, Roche and Sandoz. CD received grants, consulting and personal fees from Celgene, Roche, Sanofi, AbbVie, Janssen, Roche, Novartis and Pfizer. JS reports about grants, consulting and personal fees from AbbVie, AstraZeneca, Lilly, Novartis, Amgen, Astro, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Gilead, ILTOO, Janssen, Merck Sharp & Dohme, Novartis-Sandoz, Pfizer, Roche, Samsung and UCB. All other authors declare no competing interests. DA and JS declare that they currently have active roles as editorial board members of the journal.

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Data availability statement Anonymous participant data are available under specific conditions. Proposals will be reviewed and approved by the sponsor, scientific committee and staff on the basis of scientific merit and absence of competing interests. Once the proposal has been approved, data can be transferred through a secure online platform after the signing of a data access agreement and a confidentiality agreement. Not applicable.

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TRANSLATIONAL SCIENCE

Immune cell multiomics analysis reveals contribution of oxidative phosphorylation to B-cell functions and organ damage of lupus

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ABSTRACT

Objective Systemic lupus erythematosus (SLE) is the prototypical systemic autoimmune disease. While the long-term prognosis has greatly improved, better long-term survival is still necessary. The type I interferon (IFN) signature, a prominent feature of SLE, is not an ideal therapeutic target or outcome predictor. To explore immunological pathways in SLE more precisely, we performed transcriptomic, epigenomic and genomic analyses using 19 immune cell subsets from peripheral blood.

Methods We sorted 19 immune cell subsets and identified the mRNA expression profiles and genetic polymorphisms in 107 patients with SLE and 92 healthy controls. Combined differentially expressed genes and expression quantitative trait loci analysis was conducted to find key driver genes in SLE pathogenesis.

Results We found transcriptomic, epigenetic and genetic importance of oxidative phosphorylation (OXPHOS)/mitochondrial dysfunction in SLE memory B cells. Particularly, we identified an OXPHOS-regulating gene, *PRDX6* (peroxiredoxin 6), as a key driver in SLE B cells. *Prdx6*-deficient B cells showed upregulated mitochondrial respiration as well as antibody production. We revealed OXPHOS signature was associated with type I IFN signalling-related genes (ISRGs) signature in SLE memory B cells. Furthermore, the gene sets related to innate immune signalling among ISRGs presented correlation with OXPHOS and these two signatures showed associations with SLE organ damage as well as specific clinical phenotypes.

Conclusion This work elucidated the potential prognostic marker for SLE. Since OXPHOS consists of the electron transport chain, a functional unit in mitochondria, these findings suggest the importance of mitochondrial dysfunction as a key immunological pathway involved in SLE.

Key messages

What is already known about this subject?

⇒ Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect various organs. Both adaptive and innate immune system contribute to SLE pathogenesis, but precise mechanism of immune system regulation remains unclear. The type I interferon signature is a prominent feature of SLE, but its correlation with SLE activity is controversial and it cannot predict disease prognosis.

What does this study add?

⇒ Our transcriptomic, epigenetic and genomic analyses on 19 immune cell subsets from peripheral blood mononuclear cell of patients with SLE revealed the importance of memory B cells via oxidative phosphorylation (OXPHOS)/mitochondrial dysfunction.

⇒ By combining differentially expressed genes analysis and expression quantitative trait loci analysis, *PRDX6* (peroxiredoxin 6), one of the SLE susceptibility genes, was picked up as a candidate key driver gene for SLE pathogenesis. Mitochondrial respiration in B cells and antibody production were upregulated by *Prdx6* deficiency.

⇒ The OXPHOS signature in patients with SLE could predict long-term prognosis and was associated with certain clinical phenotypes. Additionally, we revealed that the gene set related to Toll-like receptor signalling was strongly correlated with OXPHOS signature, suggesting innate immune signal importance for SLE pathogenesis.

How might this impact on clinical practice or future developments?

⇒ Our immune cell multiomics analysis proposed OXPHOS signature along with innate immune signalling as a new treatment target in SLE B cells. Furthermore, OXPHOS signature could be a long-term prognostic marker of patients with SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disease. Although great improvement on the long-term prognosis for patients with lupus has been achieved, increased organ damage is associated with a poorer prognosis in some patients. Previous studies on SLE, including genome-wide association studies (GWAS) and gene expression studies in peripheral blood mononuclear cells (PBMCs), indicated a role of type I interferon (IFN) signalling in SLE immunological pathogenesis.[1–3] However, the type I IFN signature does

not correlate with long-term prognosis,[4–9] and although phase III trials with an antibody blocking the type I IFN pathway showed improvement of clinical activity, approximately 50% of patients with SLE did not exhibit a significant response.[10] These observations strongly suggest a pathogenic contribution from critical immunological pathways other than the classical type I IFN signature. Consistently, based on recent progress in integrated analyses, researchers have revealed a correlation between lupus nephritis activity and a plasmablast/neutrophil signature in blood.[11] Moreover, the exhausted CD8 T-cell gene signature is associated with good outcomes.[9] To advance these findings, more detailed analyses of immune cell subsets are needed because transcriptome analyses of a mixture of cell subsets are obscured by variations among the different cell types. Moreover, the subset-derived transcriptome has less variability than the single-cell-derived transcriptome and suitable for association analysis with genetic polymorphisms with higher accuracy.

In this study, we analysed the transcriptomes of 18 blood immune cell subsets and the genotypes of 107 patients with SLE and 92 healthy controls (HCs), together with open chromatin data of 8 patients with SLE and 8 HCs obtained by Assay for Transposase-Accessible Chromatin (ATAC)-seq. Our integrated analysis indicated the importance of B-cell metabolic regulation via mitochondrial function in SLE pathogenesis. In addition, we identified key driver genes (KDGs) related to mitochondrial dysfunction in the SLE B cells using expression quantitative trait loci (eQTL) analysis. Notably, gene sets related to innate immune signalling, including an oxidative phosphorylation (OXPHOS) signature, showed associations with SLE organ damage.

RESULTS

Importance of memory B cells in SLE pathogenesis via OXPHOS/mitochondrial dysfunction according to open chromatin and transcriptome analyses

We performed an integrated analysis using the study pipeline shown in figure 1A, and data quality was checked as in online supplemental figure S1A. We first evaluated the relative genetic contribution of each immune cell subset in PBMCs to SLE pathogenesis. We applied stratified linkage disequilibrium score regression (LDSC)[12] for partitioning heritability to identify SLE-relevant cell types using our transcriptomic datasets. Our transcriptomic data showed widespread perturbations in SLE-related genes, with approximately 1000 differentially expressed genes (DEGs) detected in each immune cell subset. We found an enrichment of SLE risk within these DEGs by LDSC analysis of specifically expressed genes (figure 1B). We also identified an enrichment of genes related to SLE risk within the open chromatin of B cells, especially in three memory B-cell subsets: unswitched memory B cells (USM B), switched memory B cells (SM B) and double-negative B cells (DN B) (online supplemental figure S1B). This was consistent with a previous study that demonstrated an enrichment of SLE risk in the open chromatin of whole B cells.[13] Pathway analysis of the DEGs revealed a conserved IFN signalling pathway among all immune cell subsets. With regard to B cells, we revealed a relative enrichment of DEGs related to OXPHOS and mitochondrial dysfunction pathways (figure 1C and online supplemental figure S1C). Due to an almost complete overlap of genes between the OXPHOS and mitochondrial dysfunction pathways, we used the term 'OXPHOS' in our following analyses. Using weighted gene correlation network analysis (WGCNA),[14] we determined the correlations of each module eigengene among all subsets in the test and replication cohorts (figure 1D and online supplemental figure S1D). IFN signalling modules showed a strong correlation with each other irrespective of the immune cell type. Interestingly, OXPHOS modules in USM B and SM B were correlated with these IFN signalling modules more strongly than in other cell types. This result suggests a biological relationship between these two pathways in memory B cells, consistent with previous reports showing the importance of OXPHOS in SLE.[15 16] Furthermore, transmission electron microscopy revealed an increased proportion of swollen mitochondria[17] in SLE memory B cells, but not SLE-naive B cells (figure 1E). The upregulated mitochondria-related genes did not suggest apoptosis of memory B cells in patients with SLE, because neither naive nor memory B cells in patients with SLE were proapoptotic (online supplemental figure S1E).[18] Differentiation of memory B cells into plasmablasts by stimulation with a Toll-like receptor (TLR) 9 agonist (CpG) and type I IFN[19 20] was inhibited by the administration of inhibitors of the electron transport chain (ETC) complex I or III (online supplemental figure S1F), confirming the importance of OXPHOS in plasmablast differentiation. Notably, in stimulated memory B cells, OXPHOS signature scores were induced by CpG, but not type I IFN (figure 1F), suggesting a role for innate immune signalling for inducing the OXPHOS pathway in SLE B cells.

Epigenetic regulation of the OXPHOS signature according to ATAC-seq

Next, we evaluated whether upregulation of the OXPHOS signature is associated with an open chromatin state, using ATAC-seq data. Consistent with the LDSC results in online supplemental figure S1B, differentially accessible regions were most abundant in memory B cells (online supplemental figure S2A). Next, we applied the chromVAR algorithm to our ATAC-seq datasets to investigate cell type-specific transcriptional regulation with accessibility of transcription factor (TF).[21] First, principal component analysis showed each parental immune cell type was clustered independently (online supplemental figure S2B), supporting the quality of our ATAC-seq analysis. Each B-cell subset was clustered independently, and disease status constituted distinct clusters within each B-cell subset (online supplemental figure S2C). Because the expression of ETC genes was upregulated in all B-cell subsets in patients with SLE (online supplemental figure S2D and online supplemental table S1), we evaluated the open chromatin status within the binding regions of TFs that regulate the ETC complex, including nuclear respiratory factor 1 and 2 (NRF1 and NRF2), oestrogen-related receptor alpha, yin yang 1 (YY1) and cAMP-response element binding protein (CREB).[22–24] The TF enrichment scores for NRF1, YY1, oestrogen response element, cAMP response element (CRE) and CREB1 showed a higher tendency to be present in each B-cell subset of patients with SLE (online supplemental figure S2E). The enrichment scores of YY1 in plasmablasts, CRE in naive B cells and plasmablasts, and CREB1 in naive B cells and plasmablasts showed a significant upregulation (online supplemental figure S2F).

Association between the genetic risk of SLE and an OXPHOS signature by eQTL analysis

GWAS has identified many single nucleotide polymorphisms (SNPs) associated with the risks of several autoimmune diseases. Several approaches have been taken to identify causal genes by integrating risk SNP, eQTL and transcriptomic data.[25 26] We recently constructed an eQTL database, ImmuNexUT, which consists of 336 subjects with immune-mediated diseases and 79 HCs (see online supplemental material and methods).[27] We identified some SLE susceptibility genes with *cis*-eQTL associations

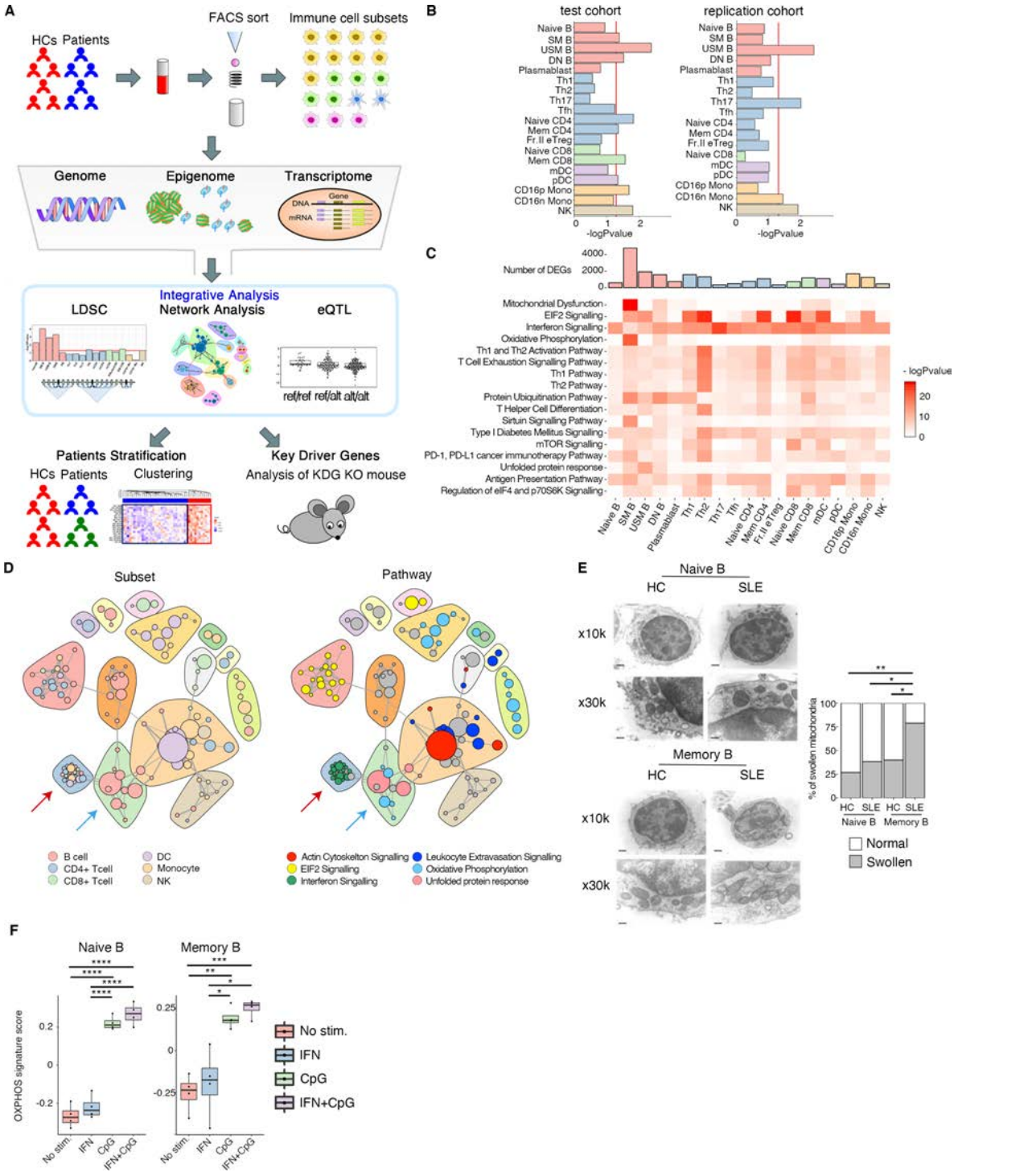

Figure 1 Overview of our analysis and identification of mitochondrial function as a key on SLE memory B cells. (A) Schematic view of the work in this study. Pipeline for collecting 19 immune cell subsets from PBMCs, and the genomic, epigenomic and transcriptomic data for the subsequent analysis. (B) Linkage disequilibrium score regression analysis of the top 1000 DEGs using summary statistics from a GWAS of SLE in each immune cell subset in both the test (left) and replication (right) cohorts. Red line indicates significance at p<0.05. (C) Pathway analysis of DEGs in all immune cell subsets with q<0.05 in the test cohort. The pathways with −log10 p-values >10 in any immune cell subset were visualised by heatmaps. (D) Network analysis of each module correlation in the test cohort. The top three pathways with high −log10 p-values that were annotated in at least two modules by ingenuity pathway analysis (IPA) were selected. Only the modules with r^2 >0.7 were visualised. The line thickness reflects the correlation strength. Red arrow indicates IFN signalling modules. Blue arrow indicates OXPHOS modules in memory B cells. (E) Transmission electron microscopy of purified naive B and memory B cells from HCs and patients with SLE. Percentages of cells with swollen mitochondria (diameter >500 nm) among 20 analysed cells are shown. (F) Human naive and memory B cells were cultured for 72 hours with combinations of CpG ODN 2006 and IFN-α. CpG ODN 2006 (2.5 µg/mL) and recombinant human IFN-α (1000 U/mL) were used. OXPHOS signature score was calculated in each condition. n=4. Student's t-test was performed. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. DEG, differentially expressed genes; GWAS, genome-wide association studies; HCs, healthy controls; IFN-α, interferon alpha; OXPHOS, oxidative phosphorylation; PBMC, peripheral blood mononuclear cell; SLE, systemic lupus erythematosus; TLR, Toll-like receptor.

(eGenes) from ImmuNexUT by assessing colocalisation of GWAS signals and eQTL signals. As this study revealed the importance of OXPHOS in SLE B cells, we picked up mitochondrial function-related 13 genes from these eGenes in B-cell subsets (figure 2A and online supplemental table S2). Within these genes, *BANK1*, *LYST* and *UBE2L3* expression showed strong correlations with the OXPHOS signature in B-cell subsets from patients with SLE (online supplemental figure S3A). These results suggest the possibility that the OXPHOS signature in B cells cooperates with genetic risk pathway in the pathogenesis of lupus.

Peroxiredoxin 6 (*PRDX6*) is a key driver gene in the B cells of patients with SLE via the regulation of mitochondrial function

Next, we attempted to identify KDGs specific to the B cells of patients with SLE referencing the KDG approach.[25] As summarised in figure 2B, we identified SLE-specific eGenes and B-cell DEGs between patients with SLE and HCs. Of the KDGs overlapping between the eGenes and DEGs (online supplemental table S3), we focused on *PRDX6* as a key gene in B cells, based on its antioxidant functions. As shown in figure 2C and online supplemental figure S4A, the eQTL effect of SLE-risk-associated SNPs led to the downregulation of *PRDX6*, suggesting that *PRDX6* expression in B cells has a protective role in SLE pathogenesis.[28] We also calculated the association between OXPHOS signature strength and *PRDX6* genotype. As shown in online supplemental figure S4B, statistically significant association was not detected in any subsets, although potential association between *PRDX6* genotype and OXPHOS signature was suggested in some subsets such as double-negative B cells.

We found a significant increase in the proportion of germinal centre B cells (GCBs) in steady-state *Prdx6* knockout (KO) mouse splenocytes (figure 2D and online supplemental figure S4C). Following primary immunisation with nitrophenyl-keyhole limpet hemocyanin (NP-KLH) in alum, the proportion of GCBs was significantly increased in *Prdx6* KO mice compared with wild-type (WT) mice, accompanied by upregulated antibody production (figure 2E,F). Splenic B cells lacking *Prdx6* demonstrated an elevated mitochondrial respiration rate (figure 2G), consistent with increased mRNA expression of ETC complex-related and OXPHOS genes in *Prdx6* KO mouse B cells (figure 2H). Mitochondrial disruption was confirmed by the significantly higher proportion of swollen mitochondria in *Prdx6* KO than in WT mouse B cells (figure 2I). These results suggest a protective role of PRDX6 in SLE pathogenesis by negatively regulating plasmablast differentiation via mitochondrial function.

OXPHOS gene signature predicts long-term prognosis and is associated with certain clinical phenotypes of SLE

To address long-term risk evaluation in SLE, we examined the associations between the OXPHOS signature and clinical parameters, including the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (SDI), in our cohort. After excluding the patients with chronic kidney disease (see Methods), 74 patients with SLE were evaluated in the following analysis. Patients in the test cohort clustered into those with high scores for the OXPHOS signature (see Methods) were significantly enriched among the patients with an SDI>0 ($p=0.03$), whereas those with high scores of the type I IFN signalling-related signature showed no enrichment among patients with an SDI>0 (figure 3A). Tendency of enrichment was maintained in the replication cohort, although it did not reach statistical significance ($p=0.08$) (online supplemental figure S5A). Concerning that the OXPHOS signature might be strongly affected by specific clinical features, we evaluated the correlation between the OXPHOS signature and some potential confounders: disease duration, SLE disease activity index-2K (SLEDAI-2K), prednisolone (PSL) dosage, titre of double-stranded DNA (ds-DNA) and estimated glomerular filtration rate (eGFR). No association between each potential confounder and OXPHOS signature reached statistical significance (online supplemental table S4).

We investigated which clinical phenotypes correlated with the OXPHOS signature and organ damage. We stratified patients with SLE with SDIs>0 from both cohorts (figure 3B). Patients with Raynaud's syndrome were significantly enriched in the patients with high OXPHOS signatures and SDIs>0. Raynaud's syndrome is a transient and peripheral vasoconstrictive response to cold temperatures. Associations between Raynaud's syndrome and neuropsychiatric signs in single-photon emission tomography analysis[29 30] were reported. Furthermore, for patients with SLE with pulmonary arterial hypertension, Raynaud's phenomenon was a risk factor for the incidence and decreased survival.[31 32] Considering these clinical linkages, potential process of vasculopathy related to innate immune signalling and OXPHOS signature may contribute to the increased SDI in our cohort.

Importance of the OXPHOS signature, in association with the type I IFN signalling signature, in plasmablast differentiation in patients with SLE

Because the OXPHOS-related module in memory B cells was associated with the IFN signalling module (figure 1D), type I IFN signalling-related genes (ISRGs) may affect the OXPHOS pathway. We evaluated the relationship between the OXPHOS signature score and the ISRGs signature score using 184 genes related to type I IFN signalling (see Methods). The OXPHOS signature score was highest in plasmablasts and was significantly correlated with the ISRGs score in memory B cells, suggesting that the OXPHOS signature is elevated during the differentiation of memory B cells to plasmablasts (figure 3C). These two signatures also showed a correlation in Th1 (T helper type 1) and memory CD8 T cells which might reflect increased mitochondrial membrane potential in the T cells of patients with SLE (online supplemental figure S5B).[15] This correlation was confirmed in the replication cohort and was not detected in the HCs (online supplemental figure S5C,D). Notably, the OXPHOS signature score was also significantly correlated with the antibody-secreting cell (ASC) signature score[33] in DN B cells and memory B cells in both cohorts (figure 3D and online supplemental figure S5E). These data indicate that elevated expression of OXPHOS signature genes in the memory B cells of patients with SLE is related to type I IFN signalling, leading to plasmablast differentiation.

A specific type I IFN signature gene set related to OXPHOS associated with SLE damage accrual

As the OXPHOS signature score showed a correlation with the ISRGs score in memory B cells (figure 3C), we evaluated our transcriptomic data using a hierarchical clustering approach to determine the specific ISRGs that are associated with OXPHOS-related genes in patients with SLE. Total six clusters were identified and the reproducibility of the clusters was validated by factor analysis (figure 4A and online supplemental figure S6A).[34] Among the six gene sets obtained (online supplemental table S5), C6 gene set showed a strong correlation with the OXPHOS signature in both cohorts in all immune cell types (figure 4B,

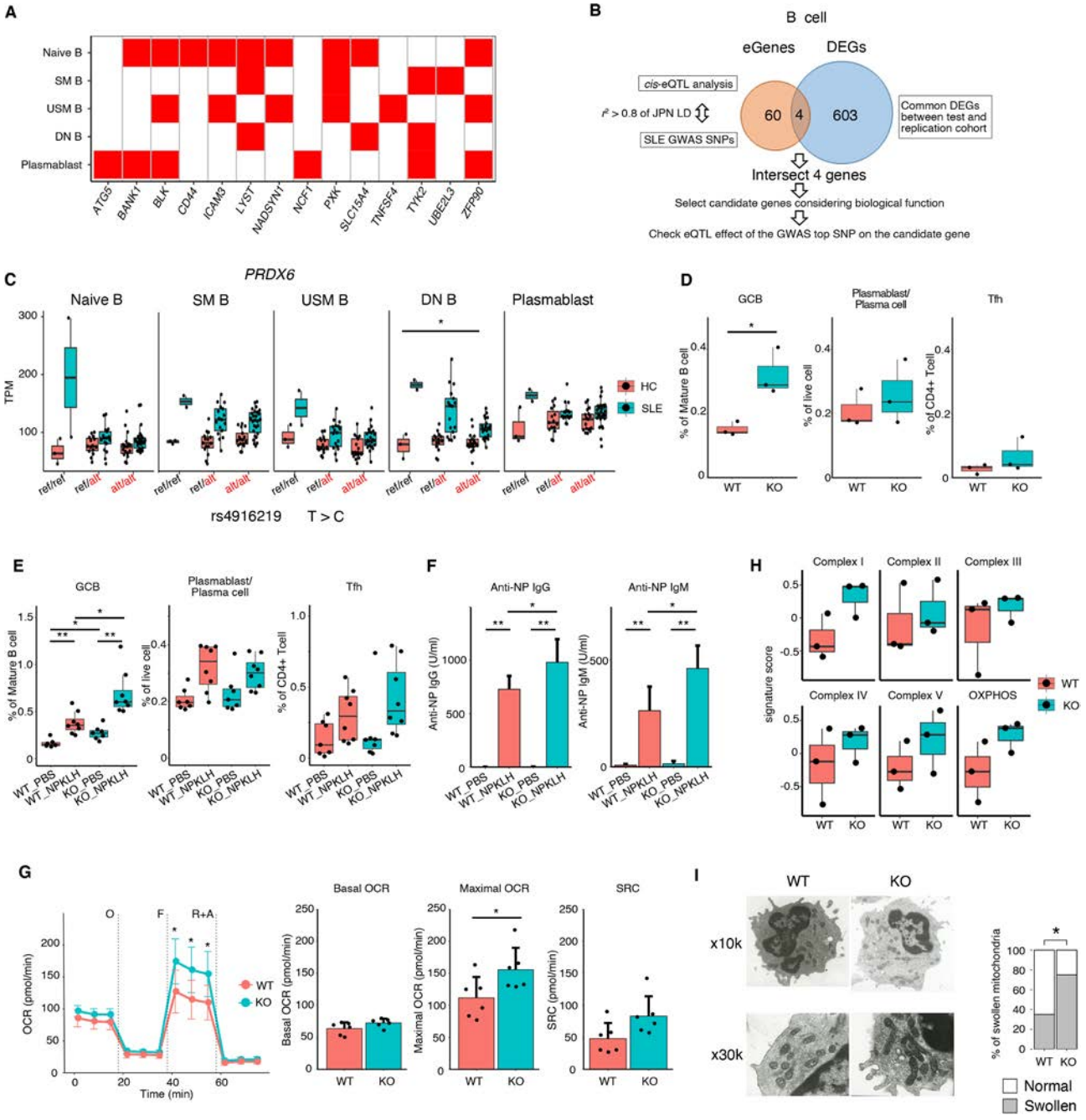

Figure 2 Identification of PRDX6 as a key driver gene in B cells of patients with SLE, and analysis of its function using knockout mice. *cis*-eQTL analysis of transcriptomic data from 79 HCs and 336 patients with IMDs using SLE GWAS catalogue SNP data and Japanese LD information as well as European LD information. (A) SLE susceptibility gene list with *cis*-eQTL effects in B-cell subsets using our IMD and HC datasets. Red colour indicates that a *cis*-eQTL effect exists. (B) Schematic diagram of identifying key driver genes in the B cells of patients with SLE. (C) *cis*-eQTL association analysis of rs4916219 for *PRDX6*. Allele C of rs4916219 of *PRDX6* was identified as a risk haplotype using GWAS data from Japanese patients with SLE. ref: reference, alt: alternative, *p<0.05, pink: HCs, turquoise: patients with SLE. (D) Analyses of GCB, plasmablast and Tfh subsets in the spleen of WT and *Prdx6* KO mice; n=3. Statistical test was performed using Student's t-test; *p<0.05. (E and F) Percentages of GCB, plasmablast and Tfh cells in the spleen (E) and anti-NP IgG and IgM production (F) in WT and Prdx6 KO mice after NP-KLH immunisation; n=8. (G) The basal OCR, maximal mitochondrial respiration rate (maximal OCR) SRC and expression of ETC complex and OXPHOS signature genes in the splenic B cells of steady-state *Prdx6* KO mice; n=6. (H) Each complex signature and OXPHOS signature scores were calculated using the splenic B cells of steady-state *Prdx6* KO and WT mice. n=3. Statistical test was performed using Student's t-test; *p<0.05. (I) Transmission electron microscopic analysis of B cells purified from the spleens of WT and *Prdx6* KO mice. The percentage of cells with swollen (>500 nm/ϕ) mitochondria among 20 cells analysed. eQTL, expression quantitative trait loci; ETC, electron transport chain; GCB, germinal centre B cell; GWAS, genome-wide association studies; HC, healthy controls; Ig, immunoglobulin; IMD, immune-mediated disease; KO, knockout; LD, linkage disequilibrium; NP, nucleoprotein; OCR, oxygen consumption rate; OXPHOS, oxidative phosphorylation; *prdx6*, peroxiredoxin 6; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism; SRC, spare respiratory capacity; Tfh, T follicular helper cell; WT, wild type.

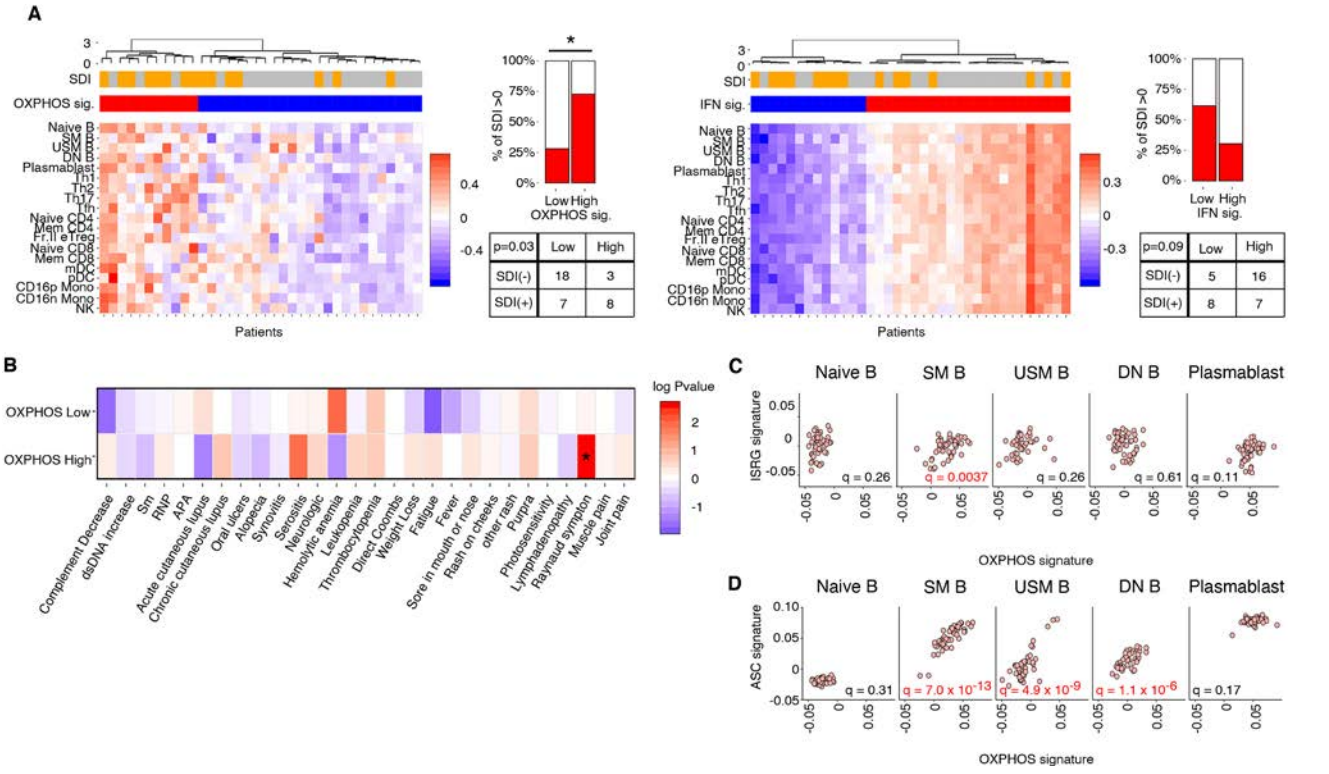

Figure 3 OXPHOS gene signature as a predictor of long-term prognosis in patients with SLE in association with clinical phenotypes and its importance in the differentiation of plasmablasts from SLE memory B cells. (A) Relationships of SDI with the OXPHOS signature score (left) and type I IFN signalling-related signature genes (ISRGs) score (right) in the test cohort (n=49). Patients with SLE without chronic kidney disease were clustered according to high- and low-scoring signatures by the hierarchical clustering method. Enrichment analysis of each patient cluster was performed with SDI>0 and =0; *p<0.05. (B) Clinical characteristics of the patients from the test and replication cohorts in the high/low OXPHOS signature clusters among the patients with SDIs>0. The data from the test and replication cohorts were combined in this analysis. Fisher's exact test was used to test for non-random associations between two categorical variables, and the signed –log10 p-values were visualised by heatmap; *p<0.05. (C and D) Correlations of the OXPHOS gene signature with type I IFN signalling-related signature (184 genes) (C) and antibody-secreting cell (D) gene signatures in SLE B-cell subsets. IFN, interferon; OXPHOS, oxidative phosphorylation; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; SLE, systemic lupus erythematosus.

online supplemental figure S6B,C). The correlations of the gene set other than C6 with the OXPHOS signature are presented in online supplemental table S6. Patients with SLE with a high C6 signature tended to be enriched among those with SDIs>0 in both test and replication cohorts (p=0.06 and p=0.09, respectively), and joint analysis of two cohorts showed significant enrichment of patients with SLE with a high C6 signature among those with SDIs>0 (p=0.02) (figure 4C). In addition, patients with high expression of C6 signature and SDIs>0 were characterised by neurological disorders (figure 4D), indicating that C6 signature predicts a risk of neurological dysfunction.

Notably, almost 50% of C6 genes were identified as DEGs in the memory B cells after CpG stimulation versus no stimulation (figure 4E). Most of these DEGs (*GBP2*, *HMGB1*, *HSP90AB1*, *HSPD1*, *IRF2*, *POLR2F*, *POLR2L*, *POLR3H*, *POLR3K*, *UBB*, *XRCC5* and *XRCC6*) were upregulated by CpG stimulation. Moreover, feature selection for neurological disorders using the Boruta algorithm in the expression data from our patients with SLE detected a significant enrichment of upregulated DEGs following CpG stimulation in memory B cells within the classifiers in naive B cells (figure 4F and online supplemental figure S6D). These observations suggest a C6 gene-mediated linkage between innate immune signalling and the progression of neurological dysfunction. Our results suggest that two gene sets related to TLR-induced signalling, OXPHOS-related genes and C6 genes, are SLE key pathways associated with damage accrual.

DISCUSSION

We present a precise cell-type-specific multiomics analyses to identify immunological pathways involved in SLE. Although a previous multiomics analysis identified several clinically meaningful linkages,[35] that analysis was performed in PBMCs or whole-blood samples, representing a combination of immunological modifications from different immune cell subsets. Although recent study on single-cell RNA sequencing of SLE PBMCs has revealed heterogeneity of immune cell subsets precisely,[36] our bulk RNA sequencing approach on as many as 18 immune cell subsets had advantages on detecting relatively low-expression genes and differences in gene expressions between each immune cell subset independent of its proportion in PBMCs. Under increasing attention to a treat-to-target approach for SLE,[37–39] a critical issue in SLE is identification of immunological pathways related to prognosis.

We identified OXPHOS-related genes as key players in SLE, particularly in memory B cells, the open chromatin status of which demonstrated the highest SLE genetic risk among the immune cell subsets. We revealed a significant association between OXPHOS signature and ASC signature. Our observation is consistent with a previous report showing that upregulation of OXPHOS using dichloroacetate increased the proportion of plasmablasts[40]; the importance of mitochondrial reactive oxygen species (mtROS) regulation in plasmablast differentiation has also been reported.[41]

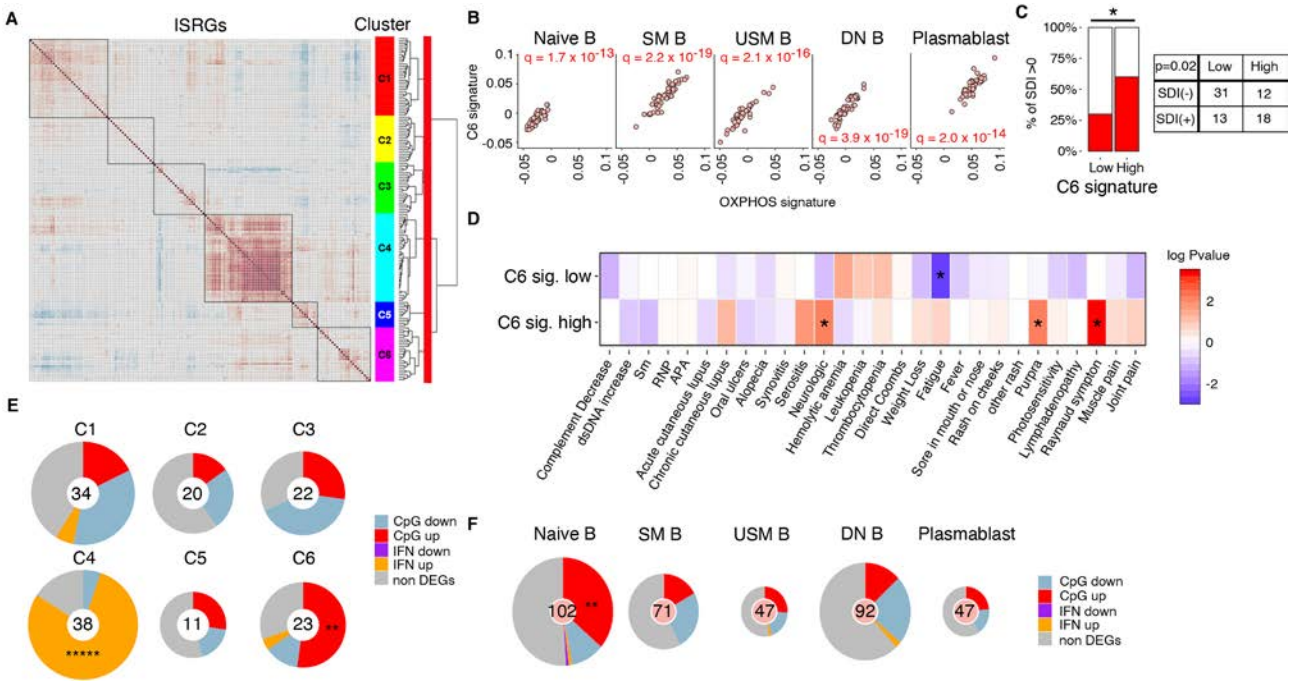

Figure 4 Identifying a specific type I IFN signalling-related gene set with a strong relationship to the OXPHOS gene signature. (A) Hierarchical clustering of 184 type I IFN signalling-related genes according to correlation coefficient of their expressions in patients with SLE from the test cohort. Six clusters (C1–C6) were identified. (B) Correlations between OXPHOS and C6 gene signatures in each B-cell subset. (C) Relationship between the C6 signature score and SDI in the test and replication cohorts. Patients with SLE without chronic kidney disease were clustered according to high- and low-scoring signatures by the hierarchical clustering method. Enrichment analysis of each patient cluster by joining both cohorts' clustering results was performed with SDI>0 and SDI=0; *p<0.05. (D) Clinical characteristics of the patients with SLE from the test and replication cohorts with high/low-scoring C6 signatures and with SDI>0. Data from the test and replication cohorts were combined in this analysis. Fisher's exact test was used to test for non-random associations between two categorical variables, and the signed –log10 p-values were visualised by heatmap; *p<0.05. (E) Relationships of each type I IFN signalling pathway gene cluster with DEGs in human memory B cells under TLR9 agonist (CpG) and type I IFN stimulation. Specific DEGs between CpG- or type I IFN-stimulated and unstimulated human memory B cells were calculated. Each gene cluster was annotated to these DEGs. Red: upregulated DEGs under CpG stimulation; blue: downregulated DEGs under CpG stimulation; orange: upregulated DEGs under type I IFN stimulation; purple: downregulated DEGs under type I IFN stimulation; **p<0.01, *****p<0.00001. (F) Feature selection using the Boruta package in RNA-seq data from 107 patients with SLE. The important features and genes in B-cell subsets for distinguishing patients with neurological disorders were selected. DEGs between CpG- or type I IFN-stimulated and unstimulated human memory B cells were calculated. Enrichments of each DEG in these classifier genes were assessed using Fisher's exact test by comparing the percentages of each DEG in whole genes analysed. Each classifier gene was annotated to these DEGs. Red: upregulated DEGs under CpG stimulation; blue: downregulated DEGs under CpG stimulation; orange: upregulated DEGs under type I IFN stimulation; purple: downregulated DEGs under type I IFN stimulation; **p<0.01. DEG, differentially expressed genes; IFN, interferon; OXPHOS, oxidative phosphorylation; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; SLE, systemic lupus erythematosus; TLR, Toll-like receptor.

The finding that several susceptible genes by a GWAS on SLE were related to mitochondrial function suggests the importance of mitochondrial function in SLE pathogenesis.[42] In addition, we identified PRDX6 as a key driver to cellular metabolism in the B cells of patients with SLE. PRDXs represent a superfamily of non-selenium peroxidases that catalyse the reduction of peroxides. Although previous studies on the function of PRDX6 in autoimmune mouse models reported controversial findings,[43–45] our *cis*-eQTL analysis and *Prdx6* KO mice indicated that PRDX6 in B cells protects against SLE. The effect size of PRDX6 on SLE pathogenesis via regulation of B cells remains to be clarified; however, the combined effect of PRDX6 impairment and activation of the innate immune system may lead to the SLE phenotype.

Regarding the clinical aspects of SLE, the OXPHOS signature was related to SDI, an indicator of damage accrual in our SLE cohorts. Oxidative stress is widely accepted as a biomarker of disease activity and organ damage in various pathologies, such as cardiovascular disease. Panousis *et al* recently reported that genes related to OXPHOS were enriched among DEGs between patients with SLE and HCs in PBMCs and were closely associated with activity and severity in SLE.[3] We also found the OXPHOS signature association with Raynaud's syndrome, which was related to mtROS in vascular smooth muscle cells,[46] and focal involvement of the central nervous system in SLE.[29 47] Our result suggested that the OXPHOS signature is associated with not only the activity of SLE but also the susceptibility of SLE supported by genetic risk. Because the OXPHOS signature in B cells was induced by TLR signalling, not type I IFN, persisting innate immune signalling even in low disease activity may influence the long-term prognosis of SLE. A recent report revealed that high IFN signalling drives changes in the mitochondrial metabolic pathways of $CD8^+$ T cells, and the metabolic rewiring observed in $CD8^+$ T cells from patients with SLE was due to the prolonged interferon alpha (IFN-α) exposure and T-cell receptor stimulation.[48] It seems that the regulation of mitochondrial metabolism and its dependency on type I IFN signalling are cell-type specific in patients with SLE. We showed no evident induction of apoptosis in SLE memory B cells under TLR stimulation that upregulates OXPHOS signature (online supplemental

figure S1E). However, some of the ISRGs strongly associated with OXPHOS signature included the apoptosis-related genes, such as HSP90AB1, HSPD1, FADD and PYCARD. This result suggested that mitochondrial dysfunction may be associated with potential induction of proapoptotic signals in SLE memory B cells.

We also identified specific TLR signalling-related genes that strongly correlate with the OXPHOS signature gene set. In terms of organ damage, a high score of these signature genes was associated with SDI and neurological disorders, again suggesting linkage between innate immune signalling and organ damage. Our observation also supports crosstalk between TLR-mediated innate immune and inflammasome signalling pathways in the pathogenesis of neuroinflammation.[49] Type I IFN production induced by TLR signalling was important for the activation of plasmacytoid dendritic cells (pDCs) by metabolic shift to increased fatty acid oxidation and OXPHOS through autocrine type I IFN-α receptor signalling.[50] TLR signalling-induced metabolic change might contribute to SLE pathogenesis not only in memory B cells but also in other immune cell subsets, such as pDCs. We have to acknowledge that we measured neither OXPHOS, oxygen consumption rate, nor mtROS in SLE B cells directly, because significant number of SLE as well as HC samples might be required to detect alterations in these measurement values. In several studies, precise assessment of metabolic status has identified immune cell-specific pathogenic modifications. MtROS and molecular modifications induced by oxidative stress in neutrophil appear to be detrimental in lupus.[51 52] Patients with SLE and lupus-prone mice present with activated and altered metabolism in $CD4^+$ T cells.[53] In the future, it is necessary to evaluate the precise metabolic state of each cell type, which is expected to lead to comprehensive evaluation of the immune system.

Several limitations of our study should be considered. The study cohort included only Asian patients who had nearly stable disease and were treated with low-dose corticosteroids. We excluded patients under high dosage of steroids because of potentially strong effects on the transcriptome, which might obscure the pathogenic changes in immune cell subsets. Therefore, our analysis may focus on a 'susceptibility' signature that persists in the presence of limited disease activity under treatment.[3]

Our multiomics approach in each immune cell type revealed the importance of OXPHOS in memory B cells for SLE progression. We suggest the clinical significance of the OXPHOS signature which was strongly associated with innate immune signalling and damage accrual in patients with SLE. We propose that innate immune signalling, including OXPHOS signature genes, as new treatment targets and long-term prognostic markers of SLE.

MATERIALS AND METHODS

See online supplemental materials and methods.

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Contributors YT performed and analysed the majority of experiments in this study. YI designed the experiments, conducted analyses, as well as wrote the manuscript. MN provided in vitro support. YN made suggestions on ATAC-seq analysis. MO performed eQTL analysis. SS, TO, KI, AS and YK provided technical assistance. KY and KF supervised the project and cowrote the manuscript. KF acted as a guarantor.

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Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by The Human Genome, Gene Analysis Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, University of Tokyo (reference no G10095). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All analysed sequencing datasets and open chromatin data, during the current study were deposited in the National Bioscience Database Center (NBDC) Human Database (http://humandbs.biosciencedbc.jp/) with the accession code hum0214, which can be downloaded on request. We used publicly available software for the analyses.

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TRANSLATIONAL SCIENCE

Peripheral blood gene expression profiling shows predictive significance for response to mycophenolate in systemic sclerosis-related interstitial lung disease

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ABSTRACT

Objectives To characterise the peripheral blood cell (PBC) gene expression changes ensuing from mycophenolate mofetil (MMF) or cyclophosphamide (CYC) treatment and to determine the predictive significance of baseline PBC transcript scores for response to immunosuppression in systemic sclerosis (SSc)-related interstitial lung disease (ILD).

Methods PBC RNA samples from baseline and 12-month visits, corresponding to the active treatment period of both arms in Scleroderma Lung Study II, were investigated by global RNA sequencing. Joint models were created to examine the predictive significance of *baseline* composite modular scores for the course of forced vital capacity (FVC) per cent predicted measurements from 3 to 12 months.

Results 134 patients with SSc-ILD (CYC=69 and MMF=65) were investigated. CYC led to an upregulation of erythropoiesis, inflammation and myeloid lineage-related modules and a downregulation of lymphoid lineage-related modules. The modular changes resulting from MMF treatment were more modest and included a downregulation of plasmablast module. In the longitudinal analysis, none of the baseline transcript module scores showed predictive significance for FVC% course in the CYC arm. In contrast, in the MMF arm, higher baseline lymphoid lineage modules predicted better subsequent FVC% course, while higher baseline myeloid lineage and inflammation modules predicted worse subsequent FVC% course.

Conclusion Consistent with the primary mechanism of action of MMF on lymphocytes, patients with SSc-ILD with higher baseline lymphoid module scores had better FVC% course, while those with higher myeloid cell lineage activation score had poorer FVC% course on MMF.

Key messages

What is already known about this subject?

⇒ The immunosuppressive agent mycophenolate mofetil has become the most commonly used treatment for systemic sclerosis (SSc)-related interstitial lung disease (ILD).

⇒ However, response to immunosuppression (cyclophosphamide or mycophenolate mofetil) is highly variable in patients with this condition.

What does this study add?

⇒ Characterisation of peripheral blood cell gene expression changes resulting from immunosuppressive treatment indicated that oral cyclophosphamide has a profound impact on immune, coagulation and erythropoiesis-related modules, while mycophenolate leads to more modest gene expression changes, including a decline in the plasmablast module.

⇒ Consistent with the primary mechanism of action of mycophenolate on lymphocytes, patients with higher baseline lymphoid modules have better per cent predicted forced vital capacity (FVC%) course on mycophenolate, while those with higher myeloid cell lineage activation score have poorer FVC% course on mycophenolate.

How might this impact on clinical practice or future developments?

⇒ Peripheral blood cell gene expression profiling might identify patients with SSc-ILD who preferentially respond to mycophenolate mofetil.

⇒ With the emergence and development of novel therapeutics for SSc-ILD, peripheral blood cell gene expression profiling may improve our ability to personalise treatment for patients in the future.

INTRODUCTION

Interstitial lung disease (ILD) is the leading cause of disease-related death in systemic sclerosis (SSc).[1 2] Scleroderma Lung Studies (SLS) I[3] and II[4] showed that both cyclophosphamide (CYC) and mycophenolate mofetil (MMF) were effective in the treatment of SSc-ILD as measured by serially obtained per cent predicted forced vital capacity (FVC%). Moreover, the recently completed Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial provided supportive data on the efficacy of background therapy with MMF as monotherapy or in combination with nintedanib in SSc-ILD.[5] MMF is the most commonly used treatment for this disease manifestation in the clinical setting.[6] However, response to immunosuppression is highly variable in SSc-ILD, with approximately one-third of patients experiencing lung volume decline despite treatment in SLS I and SLS II studies.[3 4] Moreover, CYC and MMF can be associated with serious side effects, emphasising the need for identification of likely responders.[3 4 7] However, there

are presently no widely accepted clinical or laboratory markers that can reliably predict response to immunosuppression in SSc-ILD. The recent approvals of the antifibrotic agent nintedanib[8] and the anti-interleukin (IL)-6 agent tocilizumab[9] have expanded our treatment options for SSc-ILD, but have also further underscored the unmet clinical need for better predictive biomarkers that can inform the timely initiation of the most effective treatment and prevention of irreversible lung damage.

Contrary to lung tissue, peripheral blood cell (PBC) RNA can be obtained during routine clinical care. Moreover, the availability of approved storage systems such as PAXgene and Tempus tubes has the advantage of RNA being immediately stabilised after blood draw and not affected by well-documented gene expression changes due to transport and ex vivo handling,[10 11] enabling their use in clinical setting and multicentre clinical trials. Despite its potential for clinical use, there are no previous studies examining the predictive significance of PBC RNA for response to MMF or CYC in SSc-ILD. In regard to treatment-related molecular changes, we have previously reported on PBC gene expression changes resulting from intravenous monthly CYC in SSc in the Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial,[12] but similar results have not been published for treatment with oral CYC. Moreover, there are no published reports on the impact of MMF treatment on the PBC gene expression profile of patients with SSc. Beyond its potential value as predictive biomarkers, characterisation of MMF-associated treatment effect at PBC gene expression level can provide useful molecular data for ongoing and future clinical trials in SSc, as the majority of them permit MMF background treatment.

Capitalising on the valuable PBC RNA samples collected in SLS II, we sought to characterise the PBC gene expression changes ensuing from MMF or CYC treatment and to determine the predictive significance of baseline PBC transcript scores for response to immunosuppressive treatment in SSc-ILD.

METHODS

Study participants

All SLS II patients with an available baseline PAXgene sample were included in the present study. The eligibility criteria for SLS II have been published previously[4] and key inclusion and exclusion criteria are listed in the online supplemental methods. Written informed consent was obtained from all study participants.

SLS II study design

Patients were randomised to receive either MMF for 2 years or oral CYC for 1 year followed by 1 year of placebo. Based on this design, both treatment arms were on active treatment during the first 12 months, while the participants in the MMF arm were continued on MMF therapy and those in the CYC arm were placed on placebo during the second year. Therefore, the present study focused on the analysis of gene expression changes during the first year of study during which both treatment arms were receiving active treatment. FVC% as continuous variable was the primary outcome and was measured every 3 months.

Gene expression profiling and analysis

Whole blood samples were collected in PAXgene tubes (BD Biosciences, Franklin Lakes, New Jersey) and stored at −80°C. PBC RNA was extracted according to the manufacturer's protocol. Global RNA sequencing was performed with Illumina NovaSeq 6000 (see online supplemental methods for further details). The gene expression data are deposited in the National Center for Biotechnology Information (NCBI)'s Gene Expression Omnibus.[13]

Modular analysis statistics

Modular analysis using 62 curated whole blood modules was conducted using the original repertoire analysis[14] (see online supplemental material). In addition to the traditional repertoire analysis based on the percentage of upregulated and downregulated transcripts within a module, a gene set analysis was conducted using the QuSAGE algorithm[15] for the modular analysis of differentially expressed genes. QuSAGE tests whether the average log2 fold change of a gene set is different from zero. The method correctly adjusts for gene-to-gene correlations within a gene set and provides an easily interpretable metric for the magnitude of differential regulation. A threshold value of false discovery rate (FDR) <0.05 *and* log2 fold change >0.2 was used to identify differentially expressed modules. The analysis of treatment-related changes compared each of the follow-up sample with its own baseline sample by employing a QuSAGE analysis based on linear mixed model, which took into account patient random effect. Moreover, a composite score was calculated for each module (see online supplemental methods for further details).

Determination of predictive significance of transcript modules

Joint models[16] combining a mixed effects model for the longitudinally obtained FVC% with a survival model to handle non-ignorable missing data due to study dropouts, treatment failure or death were used for each treatment arm. The joint models consisted of a linear mixed effects submodel examining FVC% from 3 to 12 months as continuous variable, with fixed effects for the baseline modular score, time (as a continuous variable in months) and baseline FVC%, with a random slope and intercept. The survival submodel was a Cox proportional hazards model predicting time to treatment discontinuation up until 12 months with terms for the modular score and baseline FVC%. Each baseline modular score (primary outcome variable of interest) was analysed in a separate model. P values for the baseline transcript score were adjusted for FDR to account for multiple comparisons, and modules with $p_{FDR<0.05}$ were defined as having predictive significance.

In an exploratory analysis, responder analyses were also performed. FVC% cut-off values previously developed based on the pooled SLS I and II data were used to define response,[17] in which the minimal clinically important difference (MCID) for improvement was an increase in FVC% >3% and the MCID for worsening was defined as FVC% decline <−3%. The FVC% measurement at 12 months compared with baseline visit was used in this analysis. In six patients with an available 9-month but missing 12-month visit measurement, the 9-month FVC% was carried forward. Logistical regression was used to determine the predictive significance of baseline modular scores for response status. Considering the loss of power with dichotomising a continuous outcome variable and the exploratory nature of this analysis, this analysis was not corrected for multiple comparison.

Patient and public involvement

This research was funded in part by the Department of Defense (DoD) Congressionally Directed Medical Research Programs, which included patient representatives in their review panels.

RESULTS

Among 142 enrolled patients, PBC RNA samples of sufficient quantity and quality for global gene expression profiling were

Table 1 Baseline patient characteristics

Characteristic	CYC, n=69	MMF, n=65	Overall, n=134
Age in years*	52.0±9.5	52.8±9.9	52.4±9.7
Female, n (%)	53 (76.8)	45 (69.2)	98 (73.1)
Race, n (%)			
White	45 (65.2)	48 (73.8)	93 (69.4)
African American	18 (26.1)	11 (16.9)	29 (21.6)
Asian	3 (4.3)	6 (9.2)	9 (6.7)
Native American	3 (4.3)	0 (0.0)	3 (2.2)
Hispanic ethnicity, n (%)	9 (13.0)	8 (12.3)	17 (12.7)
Diffuse disease type, n (%)	39 (56.5)	40 (61.5)	79 (59.0)
Disease duration in years*	2.5±1.8	2.8±1.8	2.6±1.8
FVC%*	66.0±9.9	66.5±8.2	66.3±9.1
DLCO %*	54.3±14.1	54.3±11.3	54.3±12.8
mRSS*	14.3±10.8	15.1±10.2	14.7±10.5
Antitopoisomerase I, n (%)†	30 (44.1)	28 (45.2)	58 (44.6)
Anti-RNA polymerase III, n (%)†	8 (11.8)	9 (14.5)	17 (13.1)

*Mean±SD.
†Antibody data are missing in four participants.
CYC, cyclophosphamide; DLCO%, per cent predicted diffusing capacity for carbon monoxide; FVC%, per cent predicted forced vital capacity; MMF, mycophenolate mofetil; mRSS, modified Rodnan Skin Score.

available in 134 patients at baseline (CYC=69 and MMF=65) and in 98 patients (CYC=47 and MMF=51) at the 12-month visit. As shown in table 1, baseline patient characteristics were balanced between patients assigned to CYC and MMF arms. The mean disease duration was 2.6 years and 59% of patients had diffuse cutaneous involvement in the overall patient population.

Transcript-level gene expression changes after treatment

Treatment with oral CYC led to substantial changes in PBC gene expression profile. Specifically, 6873 transcripts were differentially expressed after treatment with CYC in comparison with baseline samples. The effect of MMF on PBC gene expression was more modest, as reflected by the fact that only 113 transcripts were differentially expressed after treatment with MMF as determined by the pairwise comparison of 12-month visit samples with the baseline samples. An Ingenuity Pathway Analysis indicated that the top over-represented canonical pathways in the CYC arm were phagosome formation, ferroptosis signalling and hepatic fibrosis signalling, while the top canonical pathways in the MMF arm were primary immunodeficiency signalling, kinetochore metaphase signalling and B cell receptor signalling.

Modular gene expression changes after treatment

A previously described modular analysis method was completed.[12 14 18 19] In this analysis, 62 gene expression modules (sets of coexpressed genes) that are observed in whole blood across a variety of inflammatory and infectious diseases were investigated. Where possible, a biological function was assigned to a module based on the function of genes present in this module (eg, myeloid lineage, T cell, etc), and these modules are called annotated modules. Other modules remained uncategorised (not annotated).

The comparison of baseline samples in the CYC arm with baseline samples in the MMF arm did not yield any significant differentially expressed modules, indicating that randomisation was successful in avoiding molecular differences between the two treatment arms at enrolment (online supplemental table 1).

Table 2 Results of QuSAGE analysis for differentially expressed annotated modules in pairwise comparison of 12-month with baseline samples in the CYC arm

Module	Annotation	Log2 fold change	P_{FDR} value
M2.3	Erythropoiesis	1.21	<0.0001
M6.18	Erythropoiesis	0.93	<0.0001
M3.1	Erythropoiesis	0.91	<0.0001
M4.4	Erythropoiesis	0.57	<0.0001
M5.15	Neutrophils/granulocytes	0.53	<0.0001
M4.2	Inflammation	0.47	<0.0001
M5.3	Erythropoiesis	0.39	<0.0001
M1.1	Coagulation/platelets	0.35	0.002
M3.3	Cell cycle/proliferation	0.34	<0.0001
M3.2	Myeloid lineage	0.31	<0.0001
M6.11	Cell cycle/proliferation	0.28	0.0042
M4.14	Monocytes	0.27	<0.0001
M6.14	Coagulation/platelets	0.26	0.0001
M6.6	Myeloid lineage	0.26	<0.0001
M3.4	IFN response	0.24	0.0103
M4.6	Myeloid lineage	0.23	0.0001
M4.13	Inflammation	0.21	0.0055
M6.13	Inflammation	0.2	<0.0001
M3.6	Cytotoxic/NK cell	−0.23	0.0095
M4.3	Protein synthesis	−0.25	0.0021
M6.12	Lymphoid lineage	−0.26	<0.0001
M4.7	Lymphoid lineage	−0.3	<0.0001
M6.9	Lymphoid lineage	−0.36	<0.0001
M4.15	Cytotoxic/NK cell	−0.46	<0.0001
M6.15	T cells	−0.51	<0.0001
M6.19	T cells	−0.62	<0.0001
M4.1	T cells	−0.82	<0.0001
M4.11	Plasmablasts	−0.98	<0.0001
M4.10	B cells	−1.29	<0.0001

CYC, cyclophosphamide; FDR, false discovery rate; IFN, Interferon; NK, Natural Killer.

As listed in table 2 and shown in figure 1, the pairwise comparison of 12 months with baseline samples showed an upregulation of erythropoiesis, inflammation and myeloid lineage-related modules and a downregulation of lymphoid lineage-related modules in the CYC arm.

Consistent with the transcript-level analysis, the modular changes ensuing from MMF treatment were more modest. As shown in table 3 and figure 1, plasmablast and cell cycle modules were downregulated after MMF treatment.

Predictive significance of modular gene expression for the course of FVC

Next, composite scores were calculated for the gene expression modules shown in figure 1. Online supplemental tables 2 and 3 show the correlation/association of baseline modular scores with baseline disease duration, FVC% and modified Rodnan Skin Score (mRSS), as well as disease type and antitopoisomerase I/RNApolymerase III positivity. In this cross-sectional analysis, none of the baseline gene expression module scores was associated with baseline disease characteristics after correction for multiple comparison. Moreover, the baseline gene expression modules scores did not predict the course of mRSS during the 3-month to 12-month follow-up visits in the MMF or CYC arm (this analysis was confined to patients with diffuse cutaneous involvement) (online supplemental table 4).

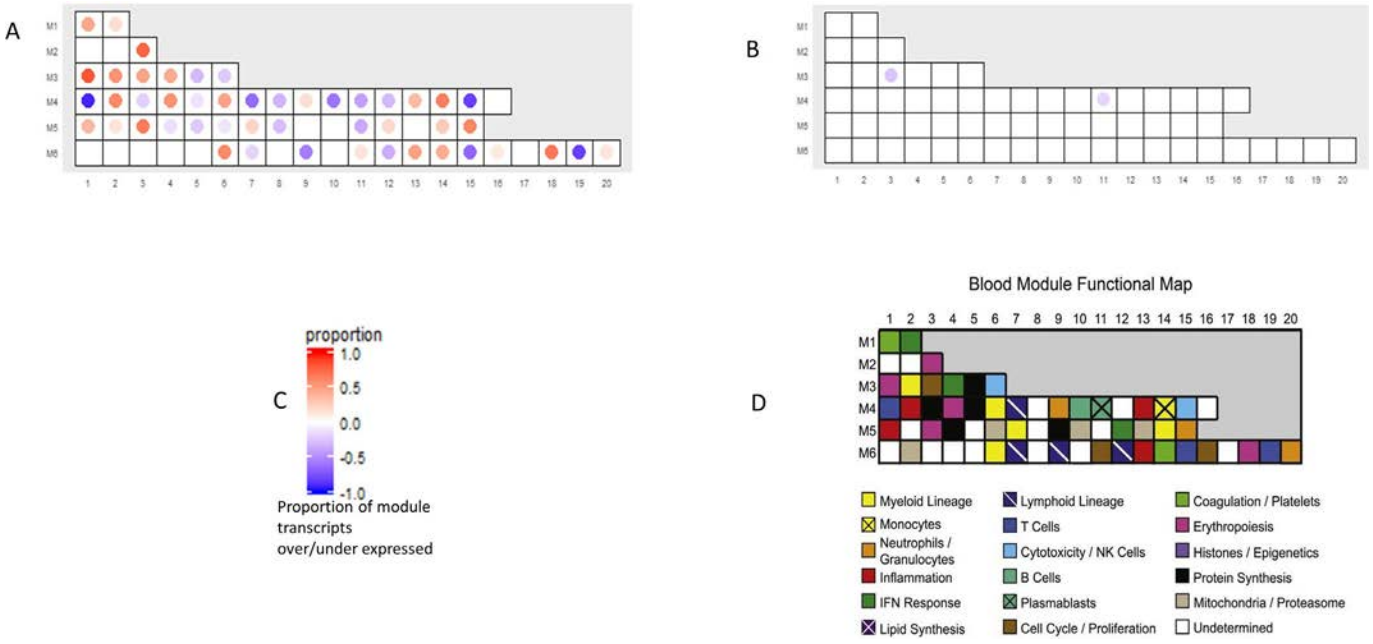

Figure 1 Differentially expressed modules in pairwise comparisons of 12-month visit with baseline SSc samples in the CYC (A) and MMF (B) arms based on traditional repertoire analysis (the percentage of upregulated and downregulated transcripts within a module). (C) Legend for the colour coding in A and B. (D) Annotation of modules based on known biological function of genes included in a given module. The numbers on y and x axes indicate the main module and submodule designation, respectively. Of note, the module map in this figure and the results in tables 2 and 3 are based on two different analytic algorithms (repertoire analysis vs QuSAGE). CYC, cyclophosphamide; MMF, mycophenolate mofetil; NK, natural killer; SSc, systemic sclerosis.

Next, the predictive significance of gene expression module scores for the course of FVC% during the 3-month to 12-month follow-up period was investigated. None of the baseline module scores significantly predicted the course of FVC% during this period in the CYC arm (online supplemental table 5). In contrast, as shown in figure 2 and listed in table 4, in the MMF arm, higher baseline lymphoid lineage (including T cells and cytotoxic/natural killer (NK) cells), as well as mitochondrial and protein synthesis modules, showed predictive significance for a better subsequent FVC% course, while higher baseline myeloid lineage (including neutrophils/granulocytes) and inflammation modules showed predictive significance for a worse subsequent FVC% course. For example, a one-unit higher baseline lymphoid lineage modular score (corresponding to an increase of one unit in the averaged Z-scores of transcript contained in the module) was associated with 2.85% higher FVC% during the 3-month to 12-month visits. A complete list of transcript modules and their predictive significance is provided in online supplemental table 5.

In an exploratory responder analysis based on previously defined MCID values,[17] 52 participants were defined as improvers (FVC% increase >3%), while 64 participants were categorised as non-improvers. Consistent with the primary analysis, patients with higher lymphoid lineage and mitochondrial module scores were more likely to have FVC% improvement, while those with higher myeloid lineage, neutrophil/granulocyte and inflammation modules were less likely to have an improvement in the MMF arm (table 5). For example, a one-unit increase in the lymphoid module score predicted 3.6 times higher likelihood of having an improvement in FVC% in the MMF arm.

Table 3 Results of QuSAGE analysis for differentially expressed annotated modules in pairwise comparison of 12-month with baseline samples in the MMF arm

Module	Annotation	Log2 fold change	P_{FDR} value
M3.3	Cell cycle	−0.43	<0.0001
M6.11	Cell cycle/DNA repair	−0.39	0.0003
M4.11	Plasmablast	−0.77	<0.0001

FDR, false discovery rate; MMF, mycophenolate mofetil.

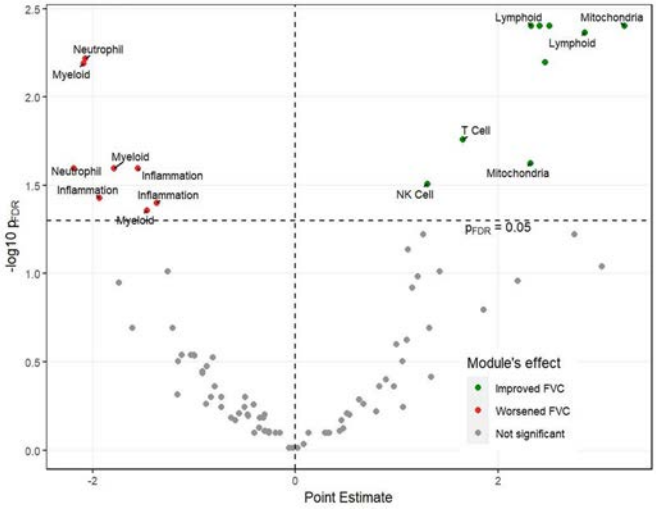

Figure 2 Predictive significance of baseline modular scores for FVC% during visits at 3–12 months in the MMF arm. Higher lymphoid module scores showed predictive significance for better ILD course, while higher neutrophil/myeloid lineage module scores showed predictive significance for worse ILD course. Of note, the modular analysis method can assign the same biological function to multiple modules. All annotated modules in figure 1 are included in this figure. FDR, false discovery rate; FVC%, per cent predicted forced vital capacity; ILD, interstitial lung disease; MMF, mycophenolate mofetil.

Table 4 Baseline annotated modular scores that showed predictive significance for the course of FVC% (as a continuous variable) during the 3-month to 12-month visits in the MMF arm*†

Module	Annotation	Point estimate	95% CI	P_{FDR} value
M5.10	Mitochondria/ proteasome	3.24	1.55 to 4.94	0.00396
M6.12	Lymphoid lineage	2.85	1.33 to 4.38	0.00434
M3.5	Protein synthesis	2.51	1.26 to 3.75	0.00396
M5.9	Protein synthesis	2.46	1.08 to 3.84	0.00639
M4.3	Protein synthesis	2.41	1.2 to 3.62	0.00396
M6.9	Lymphoid lineage	2.33	1.12 to 3.53	0.00396
M5.6	Mitochondria/ proteasome	2.32	0.8 to 3.83	0.02371
M6.19	T cells	1.65	0.61 to 2.69	0.01746
M4.15	Cytotoxic/NK cell	1.3	0.4 to 2.2	0.03106
M4.2	Inflammation	−1.37	−2.35 to −0.38	0.04002
M3.2	Myeloid lineage	−1.46	−2.53 to −0.39	0.04383
M4.13	Inflammation	−1.56	−2.6 to −0.51	0.02545
M5.14	Myeloid lineage	−1.79	−2.98 to −0.59	0.02545
M5.1	Inflammation	−1.93	−3.3 to −0.56	0.03735
M6.20	Neutrophils/ granulocytes	−2.07	−3.21 to −0.92	0.00604
M5.7	Myeloid lineage	−2.09	−3.26 to −0.91	0.00649
M4.9	Neutrophils/ granulocytes	−2.18	−3.65 to −0.72	0.02545

*Each included the listed module score (each module score separately), baseline FVC% and time as independent variables.
†Four additional not annotated modulates (M2.1, M4.12, M5.5, M6.3) showed predictive significance for the course of FVC in the MMF arm (see online supplemental table 5 for additional details).
FDR, false discovery rate; FVC%, per cent predicted forced vital capacity; MMF, mycophenolate mofetil.

In the FVC% worsening analysis (FVC% decline <−3%), 26 participants were defined as having worsening, while 90 were categorised as non-decliners. Consistent with the primary analysis, higher myeloid lineage and inflammation module scores predicted an FVC% worsening, while higher lymphoid lineage, T cell and mitochondrial modules had lower likelihood of an FVC% worsening in the MMF arm (table 6). Of note, consistent with primary analysis, none of the baseline modular scores predicted FVC% improvement or worsening in the responder analysis in the CYC arm (data not shown).

Table 5 Predictive significance of baseline annotated modular scores for improvement in FVC% (as a dichotomised variable) at 12 months in the MMF arm

Module	Annotation	OR	95% CI	P value
M5.10	Mitochondria/proteasome	3.68	1.09 to 12.44	0.0358
M6.12	Lymphoid lineage	3.63	1.21 to 10.89	0.0215
M6.9	Lymphoid lineage	2.9	1.16 to 7.26	0.0233
M4.3	Protein synthesis	2.23	1.05 to 4.71	0.0359
M3.2	Myeloid lineage	0.48	0.24 to 0.98	0.0444
M4.13	Inflammation	0.46	0.23 to 0.92	0.0277
M5.7	Myeloid lineage	0.4	0.17 to 0.92	0.0313
M6.20	Neutrophils/granulocytes	0.36	0.16 to 0.8	0.0124
M5.14	Myeloid lineage	0.35	0.16 to 0.78	0.0105

FVC%, per cent predicted forced vital capacity; MMF, mycophenolate mofetil.

Table 6 Predictive significance of baseline annotated modular scores for worsening in FVC% (as a dichotomised variable) at 12 months in the MMF arm

Module	Annotation	OR	95% CI	P value
M5.7	Myeloid lineage	5.18	1.6 to 16.78	0.006
M5.14	Myeloid lineage	4.86	1.54 to 15.29	0.0069
M5.1	Inflammation	4.65	1.43 to 15.13	0.0107
M6.20	Neutrophils/granulocytes	4.62	1.63 to 13.05	0.0039
M4.9	Neutrophils/granulocytes	3.95	1.2 to 12.99	0.0239
M4.13	Inflammation	3.36	1.36 to 8.27	0.0084
M6.13	Inflammation	3.22	1.07 to 9.74	0.0381
M3.2	Myeloid lineage	2.76	1.19 to 6.37	0.0177
M4.2	Inflammation	2.26	1.09 to 4.66	0.0275
M4.6	Myeloid lineage	2.25	1.05 to 4.79	0.0363
M4.11	Plasmablasts	0.43	0.2 to 0.97	0.0414
M6.19	T cells	0.43	0.19 to 0.96	0.04
M4.10	B cells	0.42	0.2 to 0.91	0.0267
M4.15	Cytotoxic/NK cell	0.42	0.2 to 0.84	0.0153
M6.15	T cells	0.40	0.17 to 0.96	0.041
M4.3	Protein synthesis	0.38	0.16 to 0.9	0.0281
M3.6	Cytotoxic/NK cell	0.36	0.13 to 0.98	0.0457
M5.6	Mitochondria/proteasome	0.31	0.11 to 0.91	0.0325
M3.5	Protein synthesis	0.26	0.09 to 0.69	0.0074
M6.9	Lymphoid lineage	0.25	0.09 to 0.7	0.0081
M5.10	Mitochondria/proteasome	0.20	0.05 to 0.78	0.0205
M6.12	Lymphoid lineage	0.19	0.05 to 0.64	0.0073
M6.16	Cell cycle/DNA repair	0.11	0.02 to 0.64	0.0132

FVC%, per cent predicted forced vital capacity; MMF, mycophenolate mofetil; NK, Natural Killer.

DISCUSSION

In the present study, PBC gene expression changes ensuing from CYC or MMF in patients enrolled in the SLS II were examined, showing that oral CYC had a profound impact on immune, coagulation and erythropoiesis-related modules, while MMF led to more modest gene expression changes, including a decline in the plasmablast module. We also studied the predictive significance of PBC transcript profile for response to immunosuppression in SSc-ILD, showing that patients with higher baseline lymphoid modules had better FVC% course, while those with higher myeloid cell lineage activation score had poorer FVC% course on MMF.

CYC alkylates DNA and thereby inhibits cell division. In our previous study in the SCOT trial, intravenous monthly CYC treatment led to a decline in the B cell module (4.10) and an increase in the neutrophil (5.15) module. These changes were also observed in the present study among patients treated with oral CYC. However, oral CYC also led to significant increases in the erythropoiesis, coagulation and myeloid lineage immune modules, as well as decreases in the lymphoid lineage modules. The more profound impact of CYC on the PBC gene expression profile in SLS II than in the SCOT trial may be due to higher sample size in the present study or differences in dosage and mode of administration (oral daily vs intravenous monthly). A differential impact of CYC on PBCs based on the mode of administration is supported by a recent study showing a four times higher cumulative dose of CYC and higher frequency of leucopenia with the daily oral than with the intravenous CYC administration in patients with SSc.[20] Moreover, oral CYC had a more profound impact on PBC gene expression profile than MMF in the present study. This is consistent with the clinical

observation that CYC had a worse tolerability and toxicity profile than MMF in SLS II.[4]

MMF is a prodrug of mycophenolic acid. Mycophenolic acid preferentially impairs guanosine nucleotide synthesis in T and B lymphocytes by blocking the enzyme IMPDH (inosine-5-monophosphate dehydrogenase) because it is five times more potent in inhibiting the type II isoform of this enzyme, which is expressed in activated T and B lymphocytes than its housekeeping isoform (type I), which is expressed in most cell types.[21 22] Consistent with the primary mechanism of action of MMF on lymphocytes, we observed that MMF treatment led to a decline in the plasmablast transcript module and that patients with a high lymphoid lineage gene expression profile had a better response to MMF. While there are no other published data on PBC gene expression or flow cytometry-based immune cell count changes ensuing from MMF treatment in SSc, a decline in the number of peripheral blood plasmablasts, B cells and T cells has been reported in cytometry-based studies in systemic lupus erythematosus.[23 24] The MMF-mediated downregulation of plasmablast function[23] might also explain the results of a recent study of 686 patients with autoimmune rheumatic diseases indicating MMF (along with rituximab and abatacept) treatment was associated with a significantly reduced response to COVID-19 vaccine.[25] Specifically, the seropositivity rate of patients treated with MMF was 64%, while patients treated with methotrexate, leflunomide, anti-tumour necrosis factor (TNF) and anti-IL-6 monotherapies had immune responses above 90%. Similarly, patients with solid organ transplant recipients who are treated with MMF were at higher risk of mounting an insufficient response to COVID-19 vaccination.[26–28]

A global gene expression study examining the transcript changes ensuing from MMF treatment in SSc skin reported a decline in T cell, activated dendritic cell and macrophage transcript modules based on the longitudinal assessment of six patients but not in B cell modules following treatment.[29] The discrepancy between the skin findings in the previous study and our PBC transcript results might stem from differences in SSc immune signatures at the PBC and end-organ level. Specifically, the immune signature in SSc skin is influenced by abundance of specific cell types, homing of immune cells from blood into the affected tissue and the local inflammatory cytokine milieu. For example, low abundance of B cells in the skin tissue might have contributed to the lack of B cell signature changes in the aforementioned study. Moreover, MMF can inhibit the glycosylation and function of adhesion molecules, resulting in decreased extravasation of T cells and monocytes into the affected tissue, which might in part explain the observed decline of T cell, activated dendritic cell and macrophage transcript modules in SSc skin following MMF treatment.[21 30 31]

In the present study, neither CYC nor MMF led to a decrease in the main interferon module (M1.2), which was previously reported to be the most upregulated transcript module in SSc PBCs.[12] This is consistent with our findings in the SCOT trial, in which intravenous monthly CYC, contrary to haematopoietic stem cell transplantation, did not lead to a decline in this module.[12] However, we have recently reported a composite score of 6 serum interferon inducible proteins decreased (but not normalised) with CYC and MMF treatment in SLS II.[32] This discrepancy between PBC RNA and serum protein results might stem from the fact that serum proteins are also influenced by a spillover effect from affected end organs. In fact, two recent studies indicated that the differential expression for most serum proteins in SSc was likely to originate outside PBCs.[33 34]

Our study has several strengths. Capitalising on the standardised, uniform treatment protocols in SLS II, we characterised for the first time the PBC gene expression changes ensuing from MMF treatment in SSc. Moreover, we examined for the first time the predictive significance of PBC transcripts for response to treatment in SSc-ILD, showing patients with high lymphoid lineage module scores had better FVC% course on MMF, raising the possibility that PBC gene expression profiling can potentially identify patients who would preferentially benefit from MMF. It would be informative to extend these PBC gene expression studies to valuable samples collected in the recently completed SSc-ILD trials of antifibrotic (nintedanib)[8] and anti-IL-6 (tocilizumab) agents,[9] with the ultimate goal of developing prediction models that inform the timely initiation of the most effective treatment modality.

The present study also has limitations. SLS II did not include a placebo arm during the first year of the study period. Therefore, we cannot investigate the predictive significance of aforementioned transcript modules in untreated patients with SSc-ILD. However, it is likely the observed predictive significance of baseline immune modules in the MMF arm is related to treatment effect (vs the natural history of SSc-ILD) as the same modules did not predict ILD course in the CYC arm. Moreover, the baseline PBC gene expression modules did not show predictive significance for the course of mRSS, which might be due to the fact that SLS II did not include sufficient number of patients with progressive skin involvement. It would be informative to investigate the predictive significance of the PBC modular scores for the mRSS course in future trials that are enriched for skin fibrosis progressors.

In conclusion, oral CYC has a profound impact on the PBC gene expression profile in patients with SSc-ILD, potentially accounting for the higher known toxicity.[4 20] MMF treatment leads to more modest gene expression changes, including a decline in the plasmablast module. The baseline PBC immune modules showed predictive significance for the course of SSc-ILD in the MMF arm. Consistent with the primary mechanism of action of MMF on lymphocytes,[21] patients with higher baseline lymphoid module scores had better FVC% course, while those with higher myeloid cell lineage activation score had poorer FVC% course on MMF. With the emergence and development of novel therapeutics for SSc-ILD, gene expression profiling may improve our ability to personalise treatment for patients in the future.

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CLINICAL SCIENCE

Baricitinib for relapsing giant cell arteritis: a prospective open-label 52-week pilot study

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ABSTRACT

Background/purpose Preclinical vascular inflammation models have demonstrated effective suppression of arterial wall lesional T cells through inhibition of Janus kinase 3 and JAK1. However, JAK inhibition in patients with giant cell arteritis (GCA) has not been prospectively investigated.

Methods We performed a prospective, open-label, pilot study of baricitinib (4 mg/day) with a tiered glucocorticoid (GC) entry and accelerated taper in patients with relapsing GCA.

Results 15 patients were enrolled (11, 73% female) with a mean age at entry of 72.4 (SD 7.2) years, median duration of GCA of 9 (IQR 7–21) months and median of 1 (1–2) prior relapse. Four (27%) patients entered the study on prednisone 30 mg/day, 6 (40%) at 20 mg/day and 5 (33%) at 10 mg/day. Fourteen patients completed 52 weeks of baricitinib. At week 52, 14/15 (93%) patients had ≥1 adverse event (AE) with the most frequent events, including infection not requiring antibiotics (n=8), infection requiring antibiotics (n=5), nausea (n=6), leg swelling (n=2), fatigue (n=2) and diarrhoea (n=1). One subject required baricitinib discontinuation due to AE. One serious adverse event was recorded. Only 1 of 14 (7%) patients relapsed during the study. The remaining 13 patients achieved steroid discontinuation and remained in disease remission during the 52-week study duration.

Conclusion In this proof-of-concept study, baricitinib at 4 mg/day was well tolerated and discontinuation of GC was allowed in most patients with relapsing GCA. Larger randomised clinical trials are needed to determine the utility of JAK inhibition in GCA.

Trial registration number NCT03026504.

Key messages

What is already known about this subject?

⇒ Giant cell arteritis (GCA) is a chronic rheumatic disease with a high frequency of relapse during glucocorticoid tapering.

⇒ Tocilizumab has been proven effective in the management of GCA; however, there was 15%–26% flare while receiving tocilizumab and approximately 50% flare following discontinuation, highlighting an unmet need for additional therapeutics.

What does this study add?

⇒ Baricitinib at a dose of 4 mg was well tolerated and showed preliminary efficacy in patients with relapsing GCA.

How might this impact on clinical practice or future developments?

⇒ Larger clinical trials are needed to assess the utility of Janus kinase-signal transducer and activator of transcription (JAK-STAT) inhibition in the management of GCA.

INTRODUCTION

Giant cell arteritis (GCA) is the most common primary systemic vasculitides in patients ≥50 years of age.[1] Glucocorticoids (GCs) have been the primary therapeutic intervention in GCA since their earliest use in the 1950s.[2] Relapse is common, occurring in 43%–79% of patients with GC tapering or discontinuation.[3–5] Though GCs have shown efficacy, ongoing use is often required with over 40% of patients still on GCs at 5 years.[4] Unfortunately, long-term use of GCs is associated with significant side effects and between 50% and 100% of patients have at least one GC-associated adverse event (AE).[3–6] Clinical trials evaluating disease-modifying agents and tumour necrosis factor (TNF)-alpha inhibitors have not demonstrated significant benefit.[7–12]

Thus far, only tocilizumab, an interleukin (IL)-6 inhibitor, has shown safety and efficacy in relapse reduction and decrease in GC requirements.[13 14] Given tocilizumab is the only currently approved treatment for GCA by the US Food and Drug Administration (FDA) and the European Commission, it has been quickly incorporated in clinical practice and included in recently updated consensus management guidelines.[15 16] While markedly improved compared with GC monotherapy, patients with GCA treated with tocilizumab still have flare rates of 15%–26%.[13 14] In addition, clinical trial and observational data have shown that at 12 months of tocilizumab therapy, 30%–47% of patients have still not achieved sustained clinical remission.[13 17] Furthermore, the length of treatment required for tocilizumab in GCA remains unknown. In the first clinical trial evaluating intravenous tocilizumab by Villiger and colleagues, 17/20 patients randomised to the treatment arm were in remission at the end of the 52-week study, of which 8 patients (47%) relapsed after a mean of 6.3 months from tocilizumab discontinuation.[14 18] The 2-year open-label

extension phase of the Giant Cell Arteritis Actemra (GiACTA) trial showed similar findings. Of patients who were in remission following 1 year of weekly subcutaneous tocilizumab, only 42% remained in tocilizumab-free and GC-free remission over the subsequent 2 years of observation.[19] Even though tocilizumab has dramatically improved the treatment of GCA, additional agents are needed to increase the therapeutic options, specifically among those for whom tocilizumab is not tolerated or who have not achieved sustained remission.

Janus kinase-signal transducer and activator of transcription (JAK-STAT) inhibition with tofacitinib (JAK1/Janus kinase 3 (JAK3) inhibitor) in patients with refractory Takayasu arteritis have shown promise in several case reports and small series.[20–25] A preclinical vascular inflammation model has demonstrated that JAK inhibition with tofacitinib suppressed innate and adaptive immunity in the arterial wall, particularly through suppression of tissue-resident memory T cells, and additionally further reduced inflammation by inhibition of vasculogenic effector pathways.[26] In addition, interferon-gamma stimulation of the JAK1/JAK2 pathway has been observed to promote macrophage recruitment to ex vivo cultured arteries from patients with GCA.[27] Evaluation of JAK inhibition in the clinical management of GCA, on the other hand, is sparse. Among the limited information available, baricitinib (JAK1/JAK2 inhibitor) has been used in two cases of recalcitrant GCA with beneficial outcome.[28 29] The preclinical findings and preliminary case report responses demonstrate the biological plausibility that agents selectively targeting JAK1/JAK2 hold potential promise in GCA. Although a large phase III randomised, placebo-controlled trial evaluating upadacitinib (JAK1 selective inhibitor) is ongoing (ClinicalTrials.gov identifier NCT03725202), to date, there has been no formal evaluation of safety or efficacy of JAK1/JAK2 inhibition in GCA. The purpose of this study was to evaluate the prospective safety and preliminary efficacy of baricitinib, an oral selective JAK1/JAK2 inhibitor in patients with relapsing GCA.

METHODS

Study design and patient population

This was a prospective, open-label interventional study of patients with relapsing GCA. Patients were recruited from the division of rheumatology at Mayo Clinic in Rochester, Minnesota, USA. The study was approved by the Mayo Clinic Institutional Review Board (16–0 08 993) and registered in Clinicaltrials.gov. Study definitions, which were adapted from similar GCA clinical trials, are listed in table 1.[13 30 31] All patients were required to have a prior confirmed diagnosis of GCA by either temporal artery biopsy and/or confirmatory radiographic evidence of large-vessel vasculitis (table 1). Patients were required to have a physician-confirmed relapse of GCA within 6 weeks of study entry with evidence of active disease. Relapsing patients with severe vascular symptoms, such as active visual ischaemia, aortic dissection, critical limb ischaemia, myocardial infarction or cerebrovascular event attributable to GCA were excluded. Treatment with the following agents were required to be held prior to baseline study entry: methotrexate (2 weeks), leflunomide (12 weeks), anti-IL-6 agent (4 weeks if infusible, 2 weeks if subcutaneous), rituximab (12 months), TNF-alpha inhibitor (etanercept 4 weeks, remainder of class 8 weeks) and abatacept (8 weeks). Pulse dose methylprednisolone (>100 mg/day) within 8 weeks of baseline was exclusionary as was any prior treatment of tofacitinib or other JAK-STAT inhibitor.

Study medications

During the screening phase (minimum of 2 weeks and maximum of 6 weeks), prednisone was increased to achieve symptom control prior to initiation of the study drug and subsequent accelerated GC taper. Three tiers of prednisone dose were allowed for study entry: 10, 20 or 30 mg/day. The prednisone dose of study entry was commensurate with the prednisone level at which the relapse occurred. For example, patients with a relapse

Table 1 Study definitions

Terminology	Definition
Confirmed diagnosis of GCA	Fulfilment of all of the following: ► Age ≥50 years at symptom onset. ► History of ESR ≥50 mm/hour and/or CRP ≥10 mg/L. ► Presence of at least one of the following symptoms: Unequivocal cranial symptoms of GCA (ie, new-onset localised headache, scalp or temporal artery tenderness, jaw claudication, or other unexplained mouth or jaw pain on mastication). Unequivocal symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory stiffness. Systemic inflammatory disease in which the presence of fever (>38°C for ≥7 days), weight loss (>5 lb or 10% premorbid weight) and/or night sweats attributable to GCA without other cause identified. ► Presence of at least one of the following: Temporal artery biopsy consistent with GCA. Evidence of large-vessel vasculitis by advanced arterial imaging, including magnetic resonance angiography, CT angiography, positron emission tomography–CT, or evidence of large-vessel or temporal artery findings by colour Doppler ultrasonography.
Relapse/active disease	Presence of ESR ≥30 mm/hour and/or CRP ≥10 mg/L and the presence of at least one of the following: ► Unequivocal cranial symptoms of GCA. ► Unequivocal symptoms of PMR. ► Other features judged by the clinician to be consistent with GCA or PMR (eg, fever of unknown origin, unexplained weight loss, fatigue/malaise, etc) for which no other aetiology was identified as causational.
Severe vascular symptom	► Active visual ischaemia (ie, newly developing transient or permanent vision loss or diplopia). ► Aortic dissection. ► Critical limb ischaemia. ► Myocardial infarction. ► Cerebrovascular attack attributable to GCA.
Clinical stability	Improvement in, or the absence of, ongoing signs or symptoms attributable to GCA as evidenced by a reduction in symptoms and/or an improvement in (or normalisation of) inflammatory markers.

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; PMR, polymyalgia rheumatica.

with prednisone doses of ≥20 mg but <30 mg/day were allowed to have prednisone increase to at least 30 mg/day, but not to exceed 40 mg/day for symptom control. Similarly, patients with relapse that occurred with prednisone of ≥10 mg/day but <20 mg/day had an increase to at least 20 mg/day but not to exceed 30 mg/day, and patients with relapse occurring with prednisone dose of 0 to <10 mg/day were allowed a reinstitution or increase in prednisone to at least 10 mg/day but not exceeding 20 mg/day. All patients were required to have a minimum of 2 weeks of clinical stability at their entry-level prednisone dose before study drug initiation and accelerated GC tapering. The accelerated GC taper is outlined in online supplemental table S1. GC discontinuation was at weeks 22, 19 and 15 for tiered entry of 30, 20 and 10 mg, respectively. On study entry, all participants received baricitinib 4 mg/day. Baricitinib was dispensed from a central pharmacy. Pill counts were completed at each visit to assess compliance.

Data collection and outcome measures

Laboratory parameters (complete blood count with differential, alanine aminotransferase, creatinine with estimated glomerular filtration rate (eGFR), erythrocyte sedimentation rate (ESR) and C reactive protein (CRP)), physical examination and disease activity assessment were performed at each visit (weeks 0, 4, 8, 16, 24, 32, 40 and 52). Fasting lipid profile was checked at baseline and week 16. The primary outcome was the frequency of AEs and serious adverse events (SAEs) at week 52. Definitions of AE and SAE are listed in online supplemental table S2. Parameters used for temporary hold and permanent discontinuation of baricitinib are outlined in online supplemental table S3.

Secondary outcomes included relapse (table 1) at week 24, relapse at week 52, change in pre-enrolment ESR and CRP compared with week 24 and week 52, comparison of GC dose at enrollment to week 24 and week 52. The Birmingham Vasculitis Activity Score (BVAS) V.3 was assessed at weeks 0, 24 and 52.[32] A patient global assessment was obtained at baseline and each study visit using a visual analogue scale of 100 mm length with perceived level of symptoms attributable to GCA from ranging from 0 (none) to 100 (maximum).

Statistical analysis

Descriptive statistics (eg, means, median and percentages) were used to summarise the data. Paired comparisons of measures at different timepoints were performed using paired t-tests. Measures that were not normally distributed and did not have symmetric differences were compared using sign tests. Analyses were performed using SAS V.9.4.

RESULTS

Patient characteristics

Nineteen patients were screened for this study, all of which met the initial inclusion criteria. During the screening phase, four patients were excluded: one developed active infection requiring antibiotics; one had two consecutive indeterminate tuberculosis tests; and two patients subsequently declined participation due to travel difficulty. No patients were excluded during the screening phase due to lack of clinical stability prior to study entry. Fifteen patients (100% white, 73% female) were enrolled in the study with a mean±SD age at entry of 72.4±SD 7.2 years), a median duration of GCA of 9 (IQR 7–21) months, and a median of 1 (IQR 1–2) prior relapse before study entry. Mean±SD body mass index at study entry was 26.3±3.4 kg/m^2. Thirteen (87%) patients had received historical herpes zoster (HZ) live-attenuated viral vaccine prior to screening; 1 patient received recombinant, adjuvanted HZ vaccine after study entry; and 1 patient remained unvaccinated. Characteristics at GCA diagnosis and at relapse prior to study entry are listed in table 2.

All patients had received GC for initial treatment at GCA diagnosis with only one (patient 5) off of prednisone at the time of relapse prior to study entry. Other previous agents included methotrexate (2, 13%); cyclophosphamide (1, 7%); and sirukumab (1, 7%). No patient had previously received tocilizumab. Four (27%) patients entered the study on prednisone 30 mg/day, 6 (40%) at 20 mg/day and 5 (33%) at 10 mg/day (table 2).

Safety

One patient (patient 1) with baseline chronic kidney disease (entry eGFR 51 mL/min/1.73 m2) had a decline in renal function at week 4 to a level below study threshold for continuation (eGFR 40 mL/min/1.73 m^2), and though improvement in renal function occurred with temporary hold (eGFR 48 mL/min/1.73 m^2), the patient did not have an increase to a level allowing resumption after 4 weeks of holding and therefore was prematurely withdrawn at week 8. The remaining 14 patients completed all 52 weeks of baricitinib treatment.

At week 52, 14/15 (93%) patients had at least one AE recorded with the most frequent events, including infection not requiring antibiotics (n=8), infection requiring antibiotics (n=5), nausea (n=6), leg swelling (n=2), fatigue (n=2), diarrhoea (n=1) and abdominal pain (n=1). One patient developed symptomatic HZ, which resolved within 2 weeks of holding the study drug and treatment with antiviral, allowing for subsequent reinitiation. Two patients contracted COVID-19 during the study, both with mild symptoms; neither required hospitalisation.

Only one patient had an SAE during the study (transient thrombocytopenia $<75\times10^9$/L attributed to concomitant use of antiviral). No patients had any of the following during the study: gastrointestinal perforation, major cardiovascular event (MACE), venous thromboembolism (VTE) or severe vascular symptom.

Changes in laboratory parameters at weeks 24 and 52 compared with baseline are outlined in table 3. Compared with week 0, haemoglobin, leucocytes, neutrophils and lymphocytes were lower at weeks 24 and 52. At baseline, nine patients were already receiving statin medications for non-GCA indications. Alterations in the cholesterol profile were observed at week 16 with a statistically significant increase in low-density lipoprotein (LDL) and decrease in high-density lipoprotein (HDL), but triglycerides and total cholesterol were not significantly different (table 4).

Efficacy

Only 1 of 14 (7%) patients relapsed during the study (same patient at weeks 24 and 52). The subject (patient 10) relapsed at week 24 while on 0 mg/day prednisone with recurrent headache, scalp tenderness, PMR and increased inflammatory markers. Baricitinib was continued and prednisone increased to a dose of 20 mg/day, which resulted in symptom and laboratory control. Prednisone was then tapered down to 7.5 mg/day by week 52, at which time the second relapse occurred with recurrent headache, fatigue, weight loss and increased inflammatory markers. The remaining 13 patients were able to follow the accelerated GC taper, achieve GC discontinuation and remained in disease remission during the duration of the 52-week study. No vision loss or severe vascular symptoms were present as a relapse while receiving baricitinib. Additional study outcomes

Table 2 Characteristics of patients at GCA diagnosis and at relapse prior to study entry

Patient	Sex	GCA features at diagnosis	Method GCA diagnosis	Relapse (n)	CRP (mg/L) at PSR*	ESR (mm/hour) at PSR*	GCA features at PSR*	SSA at/prior to PSR*	Prednisone (mg/day) entry tier
1	M	CSx, HA, PMR, ST	TAB (+)/LVI (–)	3	19.8	7	CSx	–	10
2	M	HA, ST	TAB (+)/LVI (–)	1	21	49	HA, PMR	–	10
3	F	CSx, LVV, PMR	TAB (+)/LVI (+)	2	23.7	71	PMR	CYC, MTX†	20
4	F	CSx, LVV, PMR	TAB (–)/LVI (+)	1	34.4	27	CSx, PMR	–	20
5	F	CSx, HA, LVV, PMR, ST	TAB (–)/LVI (+)	2	13.6	62	PMR	SIR‡	10
6	F	CSx, LVV, PMR	TAB (–)/LVI (+)	1	22.9	22	CSx, progressive LVV§	–	20
7	F	CSx, HA, JC, LVV, ST,	TAB (+)/LVI (+)	1	26.1	42	CSx, progressive LVV§	–	10
8	M	CSx, LVV, PMR	TAB (ND)/LVI (+)	2	40.6	56	CSx, PMR, progressive LVV§	MTX¶	20
9	F	CSx, HA, JC, LVV, ST	TAB (+)/LVI (+)	2	12.9	33	HA, ST	–	10
10**	F	HA, JC, ST, VI	TAB (+)/LVI (–)	1	25.6	46	HA, ST	–	30
11	M	HA, ST, VI	TAB (+)/LVI (–)	2	26	24.4	HA, ST	–	30
12	F	CSx, HA, JC, LC, LVV, PMR, ST, VI	TAB (+)/LVI (+)	2	19.2	17	CSx, PMR, progressive LVV§	–	30
13	F	CSx, HA, JC, LVV	TAB (–)/LVI (+)	1	19.3	19	CSx, HA	–	30
14	F	HA, JC, ST, VI	TAB (+)/LVI (–)	1	26.8	14	JC, PMR	–	20
15	F	CSx, HA, JC, LVV, ST	TAB (+)/LVI (+)	1	12.1	51	CSx, HA, PMR	–	20

LVI, that is, CTA, MRA, PET and PET-CT.
*PSR refers to the relapse immediately prior to study entry.
†Patient 3: CYC (oral 2 mg/kg/day×7 months) followed by MTX (oral 15 mg/week×9 years) stopped 9 months prior to PSR.
‡Patient 5: SIR (50 mg subcutaneous every 4 weeks×8 months), stopped 8 months prior to PSR.
§Progressive LVV refers to radiographic worsening of existing arterial segment or involvement of new arterial segment by LVV.
¶Patient 8: MTX (oral 20 mg/week×9 months), on treatment at PSR, held 6 weeks before entry.
**Patient 10 is the sole patient to relapse during the study (weeks 24 and 52).
CRP, C reactive protein; CSx, constitutional symptoms; CTA, CT angiography; CYC, cyclophosphamide; ESR, erythrocyte sedimentation rate; F, female; GCA, giant cell arteritis; HA, headache; JC, jaw claudication; LC, limb claudication; LVI, large-vessel imaging; LVV, large-vessel vasculitis; M, male; MRA, magnetic resonance angiography; MTX, methotrexate; ND, not done; PET, positron emission tomography; PMR, polymyalgia rheumatica; PSR, prestudy relapse; SIR, sirukumab; SSA, steroid-sparing agent; ST, scalp tenderness; TAB, temporal artery biopsy; VI, visual ischaemia.

are highlighted in table 5. ESR and CRP were both significantly lower at weeks 24 and 52 compared with pre-enrolment values. Patient global assessment at week 0 (median 20, IQR 0–50) was also significantly improved at both week 24 (median 0, IQR 0–10, p=0.022) and week 52 (median 5, IQR 0–10, p=0.039). Among patients completing the study, 4/14 (29%) flared during the 12-week follow-up period after baricitinib discontinuation.

DISCUSSION

This report constitutes the first prospective trial using an oral JAK1/JAK2 inhibitor in the management of GCA. The results of this open-label pilot study demonstrate baricitinib at a dose of 4 mg/day appeared both safe and potentially effective in the treatment of patients with relapsing GCA.

Baricitinib at a dose of 4 mg/day appeared to have sufficient control over subsequent relapse both during accelerated GC tapering and also following GC discontinuation, with only one patient (7%) having a flare while receiving the study drug. Formal clinical trials in GCA have had varying endpoints and approaches to GC tapering. Among trials with defined, accelerated, GC-tapering regimens completing at or before 28 weeks, the frequency of relapse in the placebo arms has ranged between

Table 3 Laboratory parameter changes comparing weeks 0, 24 and 52 for 14 patients

Laboratory parameter*	Week 0	Week 24	Week 52	Difference, weeks 24–0 (95% CI)	P value	Difference, weeks 52–0 (95% CI)	P value
Haemoglobin (g/L)	134±7.7	129±11.4	126±11.7	–5.1 (–9.6 to –0.6)	0.030	–8.5 (–13.1 to –3.9)	0.002
Leucocytes ($\times10^9$/L)	9.9±2.7	6.6±1.9	6.0±1.4	–3.34 (–4.74 to –1.94)	<0.001	–3.94 (–5.03 to –2.85)	<0.001
Lymphocytes ($\times10^9$/L)	2.4±0.67	1.7±0.34	1.6±0.41	–0.64 (–1.12 to –0.16)	0.012	–0.77 (–1.08 to –0.46)	<0.001
Neutrophils ($\times10^9$/L)	6.5±2.8	4.0±1.4	3.6±1.1	–2.52 (–4.07 to –0.98)	0.004	–2.12 (–4.06 to –1.71)	<0.001
Platelets ($\times10^9$/L)	290±76	324±129	312±88	34.1 (–20.0 to 88.3)	0.20	22.7 (–13.80 to 59.23)	0.20
ALT (U/L)	19.8±5.8	20.4±8.1	24.9±12.0	0.57 (–2.60 to 3.74)	0.70	5.07 (–1.78 to 11.92)	0.13
Creatinine (mg/dL)	0.9±0.13	0.9±0.13	0.9±0.20	0.02 (–0.05 to 0.08)	0.59	0.02 (–0.07 to 0.12)	0.60
eGFR (mL/mL/1.73 m^2)	67.8±11.7	67.1±10.8	67.7±14.8	–1.50 (–7.47 to 4.47)	0.60	–0.86 (–8.83 to 7.11)	0.82

*Mean ±SD.
ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate.

Table 4 Lipid profile changes comparing baseline (week 0) to week 16 for 14 patients

Laboratory parameter*	Week 0	Week 16	Difference, week 16–0 (95% CI)	P value
Low-density lipoprotein (mg/dL)	85.8±21.3	97.6±23.1	11.9 (2.7 to 21.0)	0.015
High-density lipoprotein (mg/dL)	86.4±21.9	79.9±23.6	−6.5 (−10.6 to 2.4)	0.004
Total cholesterol (mg/dL)	193.2±33.8	197.6±29.1	4.4 (−4.0 to 12.7)	0.28
Triglycerides (mg/dL)	105.9±46.7	100.2±48.1	−5.6 (−20.2 to 8.9)	0.42

*Mean ± SD.

68% and 78%.[8 9 12 13 30] With tiered entry stratification of prednisone dosing, patients starting on 30, 20 and 10 mg discontinued prednisone at weeks 22, 19 and 15, respectively. As such, the current study constitutes the first trial where all patients were tapered off GCs earlier than 24 weeks, resulting in a prolonged time of observation off of concomitant GC therapy. The only other study with discontinuation of planned prednisone dosing at 22–24 weeks was Hoffman *et al*, evaluating adjunct infliximab in patients with newly diagnosed GCA, which resulted in observed relapse rates of 82% in the study drug arm and 75% in the placebo group.[9] Compared with patients without a prior relapse, patients with a history of relapse are more likely to have a subsequent relapse.[33] Therefore, the low observed rate of subsequent relapse among patients with known relapsing GCA, combined with the accelerated prednisone taper, indicates a perceived benefit of baricitinib in control of disease activity and warrant study in a larger clinical setting.

At least one AE was recorded in all but one patient (93%). This frequency is similar to other clinical trials performed in patients with GCA, regardless of treatment or placebo arm.[9 11–13] Specifically, the AE frequency in the tocilizumab GiACTA study was 96%–98% in treatment arms and 92%–96% in placebo arms, highlighting the high frequency of AEs in patients, in part attributable to GCs.[13] The rates of AEs in this study are similar to those observed in patients receiving baricitinib for rheumatoid arthritis (RA), despite the average age of patients in the current study being 20 years older than patients treated in the RA trials.[34–40] No new forms of treatment-emergent AEs were identified among this population.

A reduction in eGFR precluded the study completion in one patient. Alteration in renal function with slight increase in creatinine and reduction in eGFR has been observed at all dosing levels of baricitinib evaluated (ie, 1, 2, 4 and 8 mg/day).[35] Discontinuation due to renal insufficiency has occurred in 5%–6% of patients receiving 4 mg/day baricitinib in RA studies, similar to the current report.[38] The overall mean difference in creatinine observed in our study was 0.02 mg/dL at both weeks 24 and 52. This mean difference was lower than studies in RA which have shown mean changes of 0.05–0.07 mg/dL at week 24 and 0.086 mg/dL at week 52 in patients receiving 4 mg/day baricitinib.[35–37] Therefore, use of baricitinib in patients with GCA with impaired renal function should be monitored closely.

HZ occurred in one patient (7%) during study drug treatment. Rates of HZ in RA studies evaluating baricitinib at doses between 2 and 8 mg/day range between 1% and 8%, similar to the frequency observed in our cohort.[36–38 40] HZ in patients with GCA is not unique to treatment with baricitinib. Among clinical trials providing sufficient detail regarding frequency of HZ, 1/20 (5%) patients receiving abatacept, 3/34 (8%) receiving adalimumab and 2/12 (17%) receiving methotrexate developed infections.[11 30 41] JAK3 inhibition appears to have greater risk of HZ than JAK2 or selective JAK1 inhibition.[42] For patients with RA, it is conditionally recommended to vaccinate prior to initiation of tofacitinib (JAK3/JAK1 inhibitor), but guidance on other es is limited.[43] The European Alliance of Associations for Rheumatology recommendations considers vaccination against HZ in high-risk patients but does not require vaccination prior to initiation of targeted synthetic disease-modifying antirheumatic drugs.[44] In the current study, the patient developing HZ had received a live-attenuated zoster vaccination after the age of 60 years but had not received a recombinant, adjuvanted zoster vaccine prior to study entry. Larger trials are necessary to assess the relative risk of HZ in the GCA population receiving JAK inhibition and to delineate the appropriate vaccination mitigation strategies among these patients.

In RA cohorts, use of baricitinib has been associated with lipid profile alterations including a rise in both HDL and LDL.[35–38 40] In the current study, the LDL increased, but the HDL decreased from weeks 0 to 16; however, there was no significant change in the overall total cholesterol. It is possible that higher-dose GCs used in the current study, in comparison to lower doses used in the management of patients with RA, may have resulted in higher

Table 5 Study outcomes

Outcome*	Prebaricitinib relapse (n=15)	Week 0 (n=15)	Week 24 (n=14)	P value†	Week 52 (n=14)	P value†
Prednisone dose (mg/day)	–	20 (10, 30)	0 (0, 0)	<0.001‡	0 (0, 0)	0.006§
ESR (mm/hour)	33 (19, 51)	7 (6, 17)	13 (7, 19)	0.002¶	10 (5, 17)	0.022**
CRP (mg/L)	22.9 (19.2, 26.1)	3.4 (<3.0, 6.9)	<3 (<3, <3)	0.002¶	<3 (<3.0, 3.1)	<0.001**
BVAS	2 (1, 3)	–	0 (0, 0)	0.002¶	0 (0, 0)	<0.001**
Patient global assessment	–	20 (0, 50)	0 (0, 10)	0.022‡	5 (0, 10)	0.039§
Discontinued glucocorticoids	–	–	14/14 (100%)	–	13/14 (93%)	–
Relapse on study drug	–	–	1/14 (7%)	–	1/14 (7%)	–

*Median (25th percentile, 75th percentile) or n (%).
†P values obtained using sign test.
‡Comparison of values of weeks 0–24.
§Comparison of values of weeks 0–52.
¶Comparison of values of prebaricitinib relapse to week 24.
**Comparison of values of prebaricitinib relapse to week 52.
BVAS, Birmingham Vasculitis Activity Score; CRP, C reactive protein; ESR, erythrocyte sedimentation rate.

baseline lipid concentrations, thus attenuating the perceived effect of baricitinib on the cholesterol profile during follow-up. Evaluation in larger cohorts is needed to better understand the impact of baricitinib on cholesterol metabolism in this patient population. Of note, no patient required initiation of lipid-lowering agent during the study based on lipid profile alteration.

Use of JAK inhibition has gained scrutiny among older adults due to concern of possible increased risk of MACE and VTE. Initial trial safety data in patients with RA >50 years of age with at least one cardiovascular risk factor comparing use of tofacitinib to those receiving a TNF inhibitor have led the US FDA to include a boxed warning for tofacitinib indicating a higher risk of MACE and VTE among patients with RA.[45] Although these preliminary data are specific to tofacitinib, the boxed warning has been extended to include upadacitinib and baricitinib. Data pooled from nine RA studies (3492 patients with 7860 patient-years of exposure), however, showed a VTE risk of only 0.5 per 100 patient-years and no increased risk of MACE in patients with RA receiving 2 or 4 mg baricitinib per day.[46] While no VTE or MACE occurred during treatment with baricitinib in the current study, the sample size is too small extrapolate overall safety in this patient population, and thus exploration of JAK1/JAK2 inhibition in this elderly population will require appropriate caution.

SAEs were notably rare in our study, only occurring in one patient with the development of significant thrombocytopenia. This particular SAE was most likely attributable to concomitant antiviral as it occurred temporally after initiation of acyclovir and recovered following cessation. In addition, the patient restarted baricitinib after a 2-week hold and continued for another 32 weeks without further thrombocytopenia developing. Furthermore, thrombocytopenia is uncommon in the use of baricitinib as a dose-dependent increase in platelets has been observed in patients with RA receiving this therapy.[34–37]

This study must be interpreted in the context of its limitations. First, the results require external validation, given the single-centre nature of this report. Second, this was an uncontrolled, open-label study without blinded clinical assessment, and therefore the lack of blinding and a control arm raises the possibility of assessment bias. Objective assessments (laboratory parameters and physical examination findings) and subjective measures (patient and physician global assessments) were used to assess response in this study as is in keeping with clinical care and current trial formats. Given improvement was noted among all evaluated domains, the likelihood of results being from assessment bias alone is unlikely. Although BVAS was incorporated as an outcome parameter, the utility of BVAS in measuring disease activity in GCA is admittedly limited.[47] Nevertheless, it is noteworthy that, to date, there remains no validated disease activity score for GCA, which consequently limits comprehensive objective clinical assessment in this condition. Third, patients evaluated in this study all had relapsing GCA, and thus the effect of this treatment on patients with new-onset disease will require formal evaluation. Fourth, patients with severe vascular manifestations present at the time of relapse were excluded, and therefore the utility of baricitinib in this subgroup remains yet unknown. Fifth, this study was designed prior to the approval of baricitinib by the US FDA, which only approved the 2 mg/day dose for RA. The use of the 4 mg/day dose in this study was based on initial preapproval studies highlighting the 4 mg/day dosing as the optimal dosing for treatment of RA.[35] Therefore, it is not certain whether a 2 mg/day dose provides a similar treatment response. Lastly, none of the patients in this study had received or failed tocilizumab prior to study entry. The utility of baricitinib in patients refractory to tocilizumab is unknown and needs to be evaluated.

In conclusion, this single-centre, open-label study of 4 mg/day baricitinib in patients with relapsing GCA demonstrated preliminary evidence of both safety and efficacy. Larger, double-blind, placebo-controlled studies are warranted to assess the utility of baricitinib in the management of patients with GCA.

Contributors All authors were involved in drafting the article or revising it critically for important intellectual content, and approved the final version to be submitted for publication. MJK and KJW 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. Guarantor of study: MJK. Study conception and design: MJK and KJW; acquisition of data: MJK, KJW and JMJ; analysis and interpretation of data: REG, CSC, MJK, KJW, ELM, AD-G and CMW.

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Ethics approval This study involves human participants and was approved by the Mayo Clinic Institutional Review Board (16-008993) and registered in Clinicaltrials.gov. Participants gave informed consent to participate in the study before taking part.

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EPIDEMIOLOGICAL SCIENCE

Postvaccination antibody titres predict protection against COVID-19 in patients with autoimmune diseases: survival analysis in a prospective cohort

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ABSTRACT

Introduction To assess the incidence and risk factors for breakthrough COVID-19 infection in a vaccinated cohort of patients with autoimmune rheumatic diseases (AIRDs) and determine whether antibodies to receptor binding domain of spike protein (anti-RBD) serve as a reliable predictor of susceptibility to such infections.

Methods Patients with AIRDs who had completed two doses of SARS-CoV2 vaccines were included and anti-RBD antibodies were determined 4–6 weeks post the second vaccine dose and stratified into good responders (GR) (>212 IU), inadequate responders (IR) (0.8–212 IU) and non-responders (NR) (<0.8 IU). Patients who had completed a minimum of 8 weeks interval after the second dose of vaccine were followed up every 2 months to identify breakthrough infections. All sero converted patients who had contact with COVID-19 were also analysed for neutralising antibodies.

Results We studied 630 patients of AIRDs (mean age 55.2 (±11.6) years, male to female ratio of 1:5.2). The majority of patients had received AZD1222 (495, 78.6%) while the remaining received the BBV152 vaccine. The mean antibody titre was 854.1 (±951.9), and 380 (60.3%) were GR, 143 (22.7%) IR and 107 (16.9%) NR. Breakthrough infections occurred in 47 patients (7.4%) at a mean follow-up of 147.3 (±53.7) days and were proportionately highest in the NR group (19; 17.75%), followed by the IR group (13; 9.09%) and least in the GR group (15; 3.95%). On log-rank analysis, antibody response (p<0.00001), vaccine(p=0.003) and mycophenolate mofetil (p=0.007) were significant predictors of breakthrough infections. On multivariate Cox regression, only NR were significantly associated with breakthrough infections (HR: 3.6, 95% CI 1.58 to 8.0, p=0.002). In sero converted patients with contact with COVID-19, neutralisation levels were different between those who developed and did not develop an infection.

Conclusion Breakthrough infections occurred in 7.4% of patients and were associated with seronegativity following vaccination. This provides a basis for exploring postvaccination antibody titres as a biomarker in patients with AIRD.

Key messages

What is already known about this subject?

⇒ A delayed and suppressed immune response to SARS- Cov2 vaccines has been observed in patients with autoimmune rheumatic diseases (AIRD).

What does this study add?

⇒ Breakthrough infections were observed in 7.4% of our cohort of 630 patients with AIRD.

⇒ Absent antibody response to receptor binding domain of spike protein (non-responders) at 1 month postvaccination was a significant predictor of breakthrough infections (HR: 3.6, 95% CI 1.6 to 8.0)).

How might this impact on clinical practice or future developments?

⇒ Postvaccination antibody response can be used as a biomarker for successful vaccination response in patients with AIRD.

⇒ This can help prioritise a subgroup of patients with AIRDs for booster doses of the vaccine.

INTRODUCTION

Patients with autoimmune rheumatic diseases (AIRDs) form a high priority group for vaccination against SARS-CoV-2.[1] Although patients with AIRDs have been excluded from vaccine trials, there is ample proof that the vaccines are safe and efficacious in this group of patients.[2] A delayed and suppressed response to SARS-CoV-2 vaccines, predominantly mRNA vaccines, have been demonstrated in patients with AIRD, especially for those on methotrexate, mycophenolate mofetil (MMF), rituximab (RTX), abatacept and glucocorticoids.[3–7]

Despite evidence of reduced immunogenicity of vaccines in AIRDs, initial data on breakthrough COVID-19 has been reassuring. Data from two large European registries showed a breakthrough rate of less than 1% from all patients with AIRD and a single centre American study found this to be 4.7%. However, breakthrough infection was associated with a much higher risk of death (8%–13%) and post-COVID-19 sequelae (8%).[8 9] Thus, it is of utmost importance to identify and mitigate risk factors for breakthrough infections. Those at high risk may require booster vaccinations for better protection against COVID-19.

As patients with AIRDs may respond inadequately to vaccines, it is important to identify a biomarker to assess the effectiveness of vaccination. This may allow

Table 1 Baseline characteristics, N=630

Age in years, mean±SD	55.2 (±11.6)
Gender, M:F	01:05.2
Type of vaccine received (%)	
BBV152	135 (21.4)
AZD1222	495 (78.6)
Type of AIRDs (%)	
Rheumatoid arthritis	415 (65.8)
Spondyloarthritis	112 (17.7)
SLE	49 (7.7)
Vasculitis	30 (4.8)
Systemic sclerosis	18 (2.9)
Other CTD	6 (0.9)
Comorbidities (%)	179 (28.4)
Hypertension	66 (10.5)
Diabetes mellitus	77 (12.2)
Dyslipidaemia	17 (2.7)
CAD	2 (0.3)
Hypothyroidism	14 (2.2)
Cancer	1 (0.15)
BPH	1 (0.15)
Bronchial asthma	1 (0.15)
Antibody titres IU/mL, (mean±SD)	854.1 (±951.9)
Based on response (%)	
Good responders	380 (60.3)
Inadequate responders	143 (22.7)
Non-responders	107 (16.9)
Break through infections (%)	47 (7.4)
COVID-19 contact (%)	69 (10.9)
Drugs (%)	
Methotrexate	360 (57.14)
Sulfasalazine	150 (23.80)
Leflunomide	51 (8.09)
Apremilast	8 (1.3)
Lenalidomide	2 (0.31)
Azathioprine	4 (0.36)
Mycophenolate mofetil	41 (6.50)
Tacrolimus	8 (1.26)
Hydroxychloroquine	408 (64.76)
Tofacitinib	47 (7.46)
TNFi	6 (0.95)
Rituximab	18 (3)
Colchicine	26 (4.1)
Corticosteroids	102 (16.19)

AIRDs, autoimmune rheumatic diseases; AZD1222, AstraZeneca COVID-19 vaccine ("Covishield"); BBV152, Bharat Biotech COVID-19 Vaccine ("Covaxin"); BPH, benign prostatic hypertrophy; CAD, coronary artery disease; CTD, connective tissue disease; F, female; M, male; SLE, systemic lupus erythematosus; TNFi, tumour necrosis factor inhibitor.

prioritisation of patients for booster doses of the vaccine for those who have mounted an inadequate immune response. Estimation of antibodies to the receptor binding domain of the spike (anti-RBD) protein of SARS-CoV-2 is now widely available worldwide at a reasonable cost. Theoretically, it can be a robust biomarker to assess vaccination efficacy. Breakthrough infection in a cohort of healthcare workers was associated with levels of anti-RBD and neutralising antibodies.[10] Again, not all laboratories have the capacity or the finances to measure neutralising antibodies. There is limited literature available on whether (total or IgG) serum anti-RBD could predict susceptibility to breakthrough infections. Current vaccination guidelines usually advise against estimating antibody levels post-vaccination.[11] Also, there are data that even in the absence of such antibodies, cell-mediated immunity induced by vaccines might be protective against COVID-19.[12]

The two vaccines predominantly used in India are adenoviral vector-borne AZD1222 (ChAdOx1 nCoV-19, AstraZeneca COVID-19 vaccine "Covishield") and the indigenous whole-virion β-propiolactone-inactivated BBV152 (Bharat Biotech COVID-19 Vaccine ""Covaxin"). Currently, India has crossed over one billion vaccination doses.[13]

We are prospectively following up a cohort of vaccinated AIRD patients. Their antibody titres against the SARS-CoV-2 Spike protein were measured at 4–6 weeks after the second dose of COVID-19 vaccination. We have previously shown that antibody titres have a good correlation with neutralisation assays in patients with AIRD.[14] We have also explored the effects of past symptomatic COVID-19 on postvaccination humoral response.[15] Our previous work has not included assays for cell-mediated immunity. Hence, one question remained whether postvaccination antibodies titres are predictive of susceptibility to breakthrough SARS-CoV-2 infections.

Thus, we prospectively followed up our cohort of 630 patients (for whom we had determined the antibody titres) to document postvaccination breakthrough infections. This survival analysis was to determine the strength of association between antibody titres and postvaccine breakthrough infections.

METHODS

Objectives

Our objectives were to assess the incidence of breakthrough COVID-19 infection in a vaccinated cohort of patients with AIRDs and to study the relationship between anti-RBD antibody titres and serum viral neutralisation activity with the incidence of breakthrough infections.

Inclusion and exclusion criteria

Patients with AIRD who had completed both the doses of SARS-CoV2 vaccines were included from March 2021 onwards and followed up till October 2021 at the Centre for Arthritis and Rheumatism Excellence in Southern India. Patients with a prior diagnosis of COVID-19 infection were excluded to prevent confounding.

Clinical details

Demographic details, type of AIRD, immunosuppressive drugs, comorbidities, details of vaccination, were recorded. For RTX, exposure over the past 6 months was recorded as part of active treatment. The majority of our patients had received 500 mgof RTX for both induction and maintenance.[16]

Antibody assays

Serum samples for estimation of antibodies titres had been collected 4–6 weeks after the second dose of vaccine. IgG antibodies against the RBD of the spike protein were measured by ELISA using the Elecsys kit (Roche, Switzerland) as per the manufacturer's instructions. Patients who had completed a minimum of 8 weeks interval after the second dose of vaccine were followed up every 2 monthly telephonically till the end of October 2021. For the analysis, patients were classified based on their anti-SARS CoV2-S antibody titres into good responders (GR) (>212 IU), inadequate responders (IR) (0.8–212 IU) and non-responders (NR) (<0.8 IU). This was based on our previous

Table 2 Comparison of characteristics among good, inadequate and non-responders

	Good (380)	Inadequate (143)	Non (107)	P value
Age in years (mean±SD)	55.49 (±11.5)	56.4 (±11.8)	52.6 (±11.5)	0.03
Gender, M:F	01:05.2	01:05.6	01:04.7	0.9
Type of vaccine (%)				0.001
BBV152	28 (20.7)	31 (23)	76 (56.3)	
AZD1222	352 (71.1)	112 (22.6)	31 (6.3)	
AIRD (%)				
Rheumatoid arthritis	261 (62.9)	95 (22.9)	59 (14.2)	0.03
Spondyloarthritis	60 (53.6)	33 (29.5)	19 (17)	0.19
SLE	35 (71.4)	5 (10.2)	9 (18.4)	0.09
Vasculitis	15 (50)	5 (16.7)	10 (33.3)	0.05
Systemic sclerosis	7 (38.9)	3 (16.7)	8 (44.4)	0.01
Other CTD	2 (33.3)	2 (33.3)	2 (33.3)	0.37
Drugs (%)				
Methotrexate	213 (59.2)	91 (25.3)	56 (15.6)	0.17
Sulfasalazine	98 (65.3)	33 (22)	19 (12.7)	0.21
Leflunomide	31 (60.8)	14 (27.5)	6 (11.8)	0.49
Azathioprine	2 (50)	0	2 (50)	0.17
Mycophenolate mofetil	17 (41.5)	7 (17.1)	17 (41.5)	0.01
TNFi	2 (33.3)	1 (16.7)	3 (50)	0.09
Rituximab	9 (50)	3 (16.66)	6 (33.33)	0.2
Tofacitinib	22 (46.8)	16 (34)	9 (19.1)	0.11
Tacrolimus	4 (50)	1 (12.5)	3 (37.5)	0.28
Steroids	55 (53.9)	25 (21.6)	22 (24.4)	0.3
Comorbidity (%)	95 (53.07)	37 (20.67)	47 (26.25)	0.06
Breakthrough infection (%)	15 (3.9)	13 (9.1)	19 (17.8)	0.01

AIRD, autoimmune rheumatic disease; AZD1222, AstraZeneca COVID-19 vaccine; BBV152, Bharat Biotech COVID-19 Vaccine; CTD, connective tissue disease; F, female; M, male; SLE, systemic lupus erythematosus; TNFi, tumour necrosis factor inhibitor.

work where a receiver operator curve (ROC) had shown that antibody titres above 212 predicted more than 30% neutralisation by sera, with a sensitivity of 81.5% and a specificity of 83.6%.[15]

Assessment of breakthrough infections

Every patient was contacted telephonically at an interval of 2 months. Details of exposure to COVID-19 contact, testing for COVID-19, breakthrough infection and severity of the infections were recorded. A COVID-19 contact was defined as per WHO recommendations.[17] The severity of infection was categorised as asymptomatic, mild, moderate and severe as per WHO criteria[18]

Neutralisation assay

Also, all sero converted patients who had known contact with a COVID-19 case had their sera analysed for neutralisation against the delta variant of SARS-CoV-2 virion particles using the SARS-Cov2 sVNT kit (GenScript, Piscataway, New Jersey, USA). This was to determine whether the presence of neutralising capability of the antibodies could give additional information regarding susceptibility to break-through infections. As seronegative individuals are unlikely to have neutralising antibodies, they were excluded from this subgroup analysis.

Statistical analysis

Data are expressed as mean and SD or median and IQR based on the Shapiro-Wilk test for normality. Baseline characteristics were compared across the three groups (GR, IR and NR). A $p<0.05$ was deemed as statistically significant, all reported values were two sided.

For the survival analysis, 'Survival' and 'Survminer' R packages were used for the survival analyses. Kaplan-Meir (KM) survival curves were used to illustrate proportions of survival among the three groups (GR, IR and NR). Univariate analysis for age, sex, diagnosis, the vaccine used and various immunosuppressant drugs against break-through infections were analysed with the log-rank test. Drugs that were used in less than 20 individuals were not analysed. All parameters that had $p<0.10$ in the univariate analysis were included in the multivariate analysis using Cox regression. The censuring events for both the cox models and the KM models were only breakthrough infection.

RESULTS

Baseline characteristics

We studied 630 patients of AIRDs with an average age of 55.2 (±11.6) years and a male to female ratio of 1:5.2. Table 1 contains details of the cohort including the background rheumatic disease, vaccine received, comorbidities and immunosuppressants used. The majority of patients had received AZD1222 (495, 78.6%) while the remaining received the BBV152 vaccine. Around a quarter (179, 28.4%) had at least one other comorbidity beyond AIRD. Methotrexate and hydroxychloroquine were the most commonly used disease modifying anti-rheumatic drugs (DMARDs). Of 360 patients who were on methotrexate, 21 patients withheld it 1–2 weeks post-vaccination whereas the others continued it.

Response to the SARS-CoV-2 vaccine

The mean antibody titres were 854.1 (±951.9)with the majority being GR (380, 60.3%). Of the remaining, 143 (22.7%) were classified as IR and 107 (16.9%) as NR.

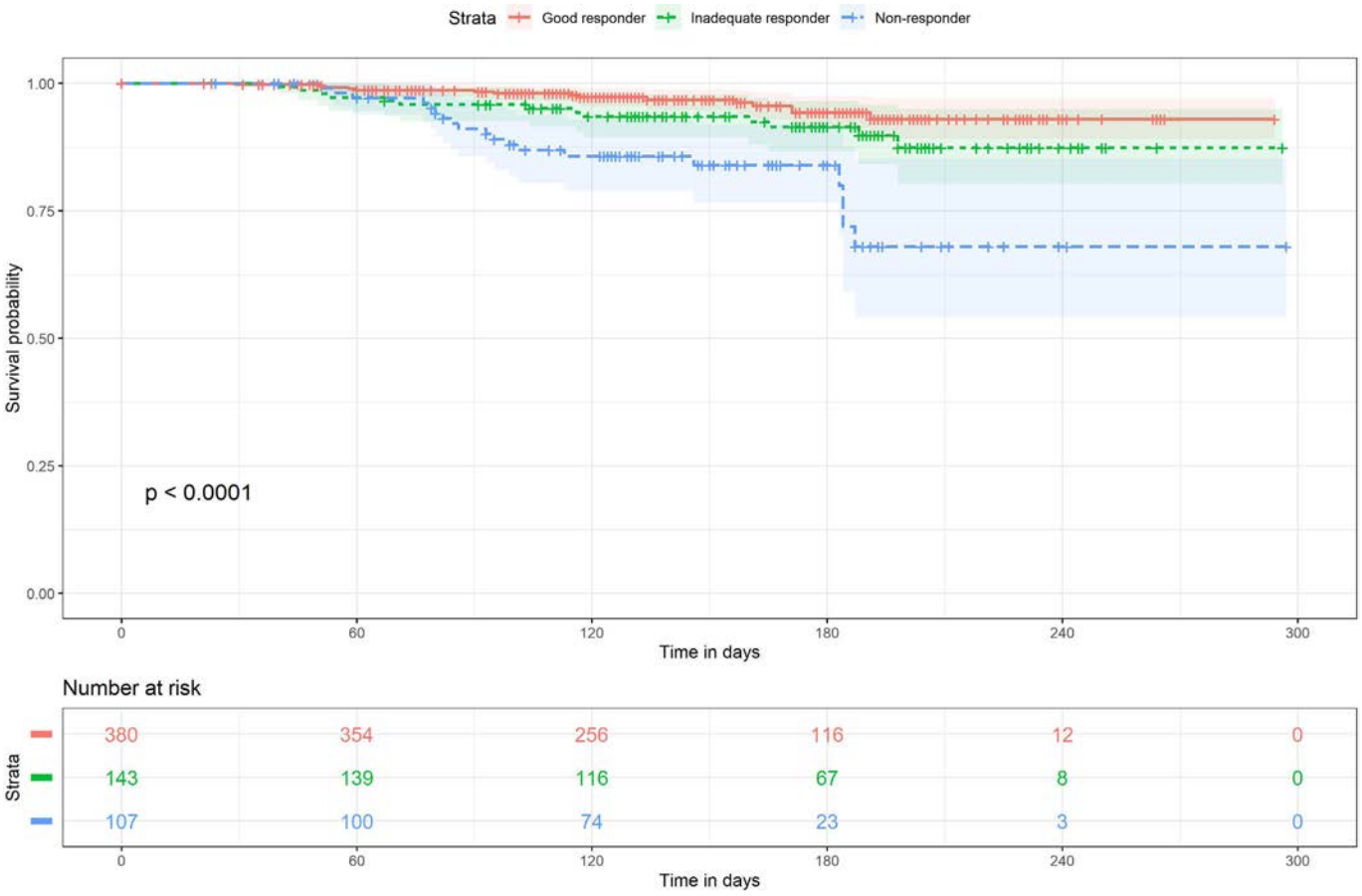

Figure 1 Kaplan-Meier survival curves for survival from breakthrough infections in three types of vaccine responders (non-responder: antibody titres <0.8 IU/mL; inadequate responder: titres 0.8–212 IU/mL; good-responders: titres >212 IU/mL).

Predictors of antibody response

On univariate analysis, the type of vaccine received was a significant determinant of response. 70% of patients developed a GR to AZD1222 whereas 56% of patients were NRs among recipients of BBV152 vaccine (p=0.001; Fisher Exact test). Based on the subtype of AIRD, the majority of patients with RA were GR (261, 62.9%) as opposed to patients with SSc (8, 44.1%) in whom the majority were NR. Systemic lupus erythematosus (SLE), vasculitis, other CTDs did not show a significant difference in the response rates.

Among the drugs, only MMF was significantly different between the three groups (table 2). Analysing antibody levels using a generalised linear model with age, disease, gender, presence of comorbidities, the vaccine used and drug usage as predictors, only the vaccine used (AZD1222 vs BVV152) and the use of methotrexate were significantly associated with lower antibody titres (online supplemental table 1).

Breakthrough infections

At a mean follow-up of 147 (±53.7) days, breakthrough infections had occurred in 47 patients (7.4%) of which 4 (8.5%) were asymptomatic, 37 (78.7%) had mild, 4 (7.4%) moderate and 2 (3.7%) severe disease. Breakthrough infections were highest in the NR group (19/107, 17.75%), followed by the IR group (13/143; 9.09%) and least in the GR group (15/380; 3.95%).

An additional 22 patients had a positive COVID-19 contact but tested negative on RT-PCR for SARS-CoV-2.

Predictors of breakthrough infections

As mentioned above, the proportion of breakthrough infections was highest in the NR group and lowest in the GR group (p=0.01; analysis of variance). The KM curve illustrating the probabilities of survival from breakthrough infection in the three groups is provided in figure 1 with overall survival of 96% for GR, 91% for IR and 82% for NR. The overlap between the 95% CIs (shaded colours) demonstrated how similar rates are between the three groups.

Online supplemental figure 1 is the KM survival curve for breakthrough infection in patients who had been administered the two different vaccines (94% for AZD1222 and 87% for BBV152). Table 3 summarises the results of univariate analysis (log-rank test) of different variables versus breakthrough infections. Univariate analysis is not reported for tacrolimus and tumour necrosis factor inhibitors since there were less than 10 patients on these drugs.

Antibody response, vaccine, gender, MMF, RTX and steroid use had an association of p<0.1 with breakthrough infection, and these were modelled in the Cox proportionate hazards regression. Figure 2 shows the HRs of which only NR was significantly associated with breakthrough infections. ROC analysis did not reveal any cut-off antibody titre that could predict breakthrough infections since the area under curve of the model was less than 0.5. This is likely because the ROC does not incorporate the time element (which determines exposure to the virus) as in survival analysis.

Table 3 Univariate analysis showing the association of the mentioned variable with postvaccination breakthrough infections

Parameter	Patients (N)	Events (COVID-19)	Log-rank test
Antibody response	GR=380	15	P<0.00001
	IR=143	13	
	NR=107	19	
Vaccine	AZD1222=495	30	P=0.003
	BBV152=135	17	
Gender	Males=102	8	P=0.9
	Females=528	39	
Comorbidities	None=451	30	P=0.4
	One or more=179	17	
Methotrexate	Yes=360	23	P=0.3
	No=270	23	
Hydroxychloroquine	Yes=408	33	P=0.4
	No=222	14	
Leflunomide	Yes=51	6	P=0.3
	No=579	41	
Tofacitinib	Yes=47	2	P=0.5
	No=583	45	
Rituximab	Yes=18	3	P=0.1
	No=612	44	
Mycophenolate mofetil	Yes=41	7	P=0.007
	No=589	40	
Sulfasalazine	Yes=150	7	P=0.1
	No=480	40	
Corticosteroid	Yes=102	13	P=0.09
	No=528	34	

AZD1222, AstraZeneca COVID-19 vaccine; BBV152, Bharat Biotech COVID-19 Vaccine; GR, good responders; IR, inadequate responders; NR, non-responders.

Neutralisation assays

Patients with a history of exposure with detectable antibodies in the sera (GR or IR) underwent estimation of virion particle neutralisation by their sera. The average neutralisation percentage by sera was significantly higher (p<0.01) for those who did not develop infection (42.9, 95% CI 16.8 to 59.6) compared with those who developed the infection (14.8, 95% CI –12.6 to 39.5) (figure 3). A minimum of 30% neutralisation by sera was achieved by 7 of 28 (25%) of those infected (despite having positive antibody titres) and 13 of 20 (65%) among those exposed but not infected had (p<0.01, OR 2.1 (95% CI 1.2 to 4.2)). The median anti-RBD antibodies were numerically higher in patients who remained negative (1091±947 IU) versus those who tested positive (654±864 IU) but the difference was not significant (p=0.08).

DISCUSSION

The cohort of 630 vaccinated patients had been divided into GR (60.3%), IR (22%) and NR (16.9%) based on their anti-RBD antibody titre 4–6 weeks postvaccination. Breakthrough infections occurred in 7.4% of patients and were associated with non-response to vaccination. This provides evidence for using post-vaccination antibody titres as a biomarker to assess successful vaccinationin patients with AIRD.

Breakthrough infections were higher (7.4%) in our study as Kerala (a state in Southern India) was facing the second wave due to delta variant during this period when the study was conducted.[13] There are two studies, one each from Europe and the United States, which reported lower breakthrough infections (<1%, 4.7%, respectively) in patients with AIRD postvaccination.[8 9] They had a similar patient profile with the most common disease subtype being RA. However, there are differences: first, most of these patients had received mRNA vaccines whereas our patients had been vaccinated with AZD1222 and BBV152 as per national guidelines and vaccine availability. Second, the majority of our patients were on oral conventional DMARDs as compared with the other two cohorts. Also, many other factors would be different between the three continents such as infection rates, population density, usage of public transportation, local travel restrictions and behavioural patterns. These factors can explain the difference in breakthrough infection rates. The severity of infection in our cohort was similar to those in the other cohort with over 90% being symptomatic.

Anti RBD antibody response to vaccines was similar to other cohorts with 16.9% being seronegative in ours as compared with 14% from Israel (post-BNT162b2 vaccine).[19] In contrast, two German cohorts reported lower rates of sero negativity (6% and 0%) post-BNT162b2 vaccine[3 6] however their sample sizes were smaller. One of the determinants of antibody response was the type of vaccine used, with poorer responses in those who received the inactivated BBV152 vaccine consistent with results previously reported in healthy controls as well as AIRD patients.[14 20 21] The number of our patients on RTX might be proportionately smaller and hence it might not reach a statistical significance due to a type 2 error. As we follow a low dose RTX protocol at our centre, most of our patients had received a lower dose of RTX which also could have contributed to a better humoral response to the vaccine. Furthermore, we have observed that patients with detectable B cells mount a good humoral response to the vaccine despite having received RTX.[16 22] However, in our cohort, the proportion of patients on MTX was higher and we interestingly found MTX to be associated with lower antibody levels even on generalised linear modelling. Other cohorts have also reported similar responses with MTX users.[3 7] Most of our patients had not withheld MTX before vaccination as there were no national or local guidelines recommending this at that time.

Our most important finding is the relationship between antibody levels and breakthrough infections. The KM curve (figure 1) demonstrates the rising probability of breakthrough infections with lower antibody levels. Though not significant in multivariate analysis, even those who had antibody titres less than the cut-off of 212 IU had numerically more infection. This implies that the antibody titre may predict risks for further infections.

Telephonic follow-up of patients at regular intervals and a state government policy of testing all the primary contacts even if they are not symptomatic enabled us to have a cohort who did not develop disease despite having a high-risk contact. Neutralisation assays were done in the subset of patients with positive antibodies who were exposed to COVID-19 as per WHO definition. The data clearly showed that COVID-19 contacts who did not develop disease had a higher proportion of neutralisation of virion particles by their sera. They also had higher titres of total antibodies though not significantly different. This might be a type II error due to limited numbers (48) in this subgroup analysis. A good correlation between neutralising antibodies and anti-RBD has been reported previously.[14 15] Though neutralisation assays may provide some additional data about susceptibility, it remains to be seen what the practical benefit of such data is.

One caveat of this study is that we have not assessed the role of T cell immunity in the protection against COVID-19. This study was not aimed at looking at T cell factors. However, antibody titres being sufficient to predict breakthrough infections

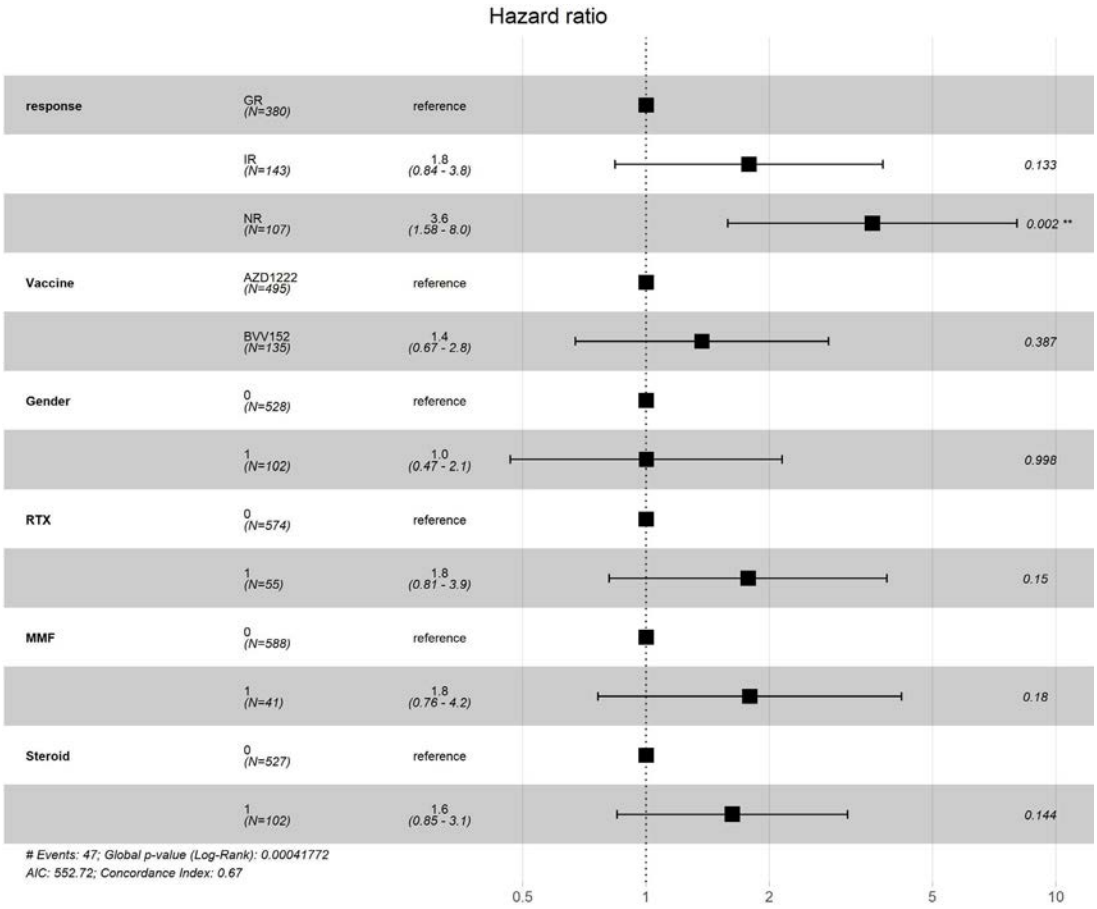

Figure 2 HRs from Cox regression modelling for survival from breakthrough infections including types of vaccine responders (non-responder: antibody titres <0.8 IU/mL; inadequate responder: titres 0.8–212 IU/mL; good-responders: titres >212 IU/mL), gender (1=male), rituximab (RTX=1 implies exposure within last 6 months), mycophenolate mofetil (MMF=1 implies exposure within the last 3 months of vaccination) and steroid use (1=any steroid use within 3 months of vaccination). GR, good responders; IR, inadequate responders; NR, non-responders.

do not exclude the role of T cells. T cell responses may go hand in hand with humoral responses.[12] What is more relevant in the clinical context is that the antibodies alone are sufficient as a biomarker for the risk of future infections.

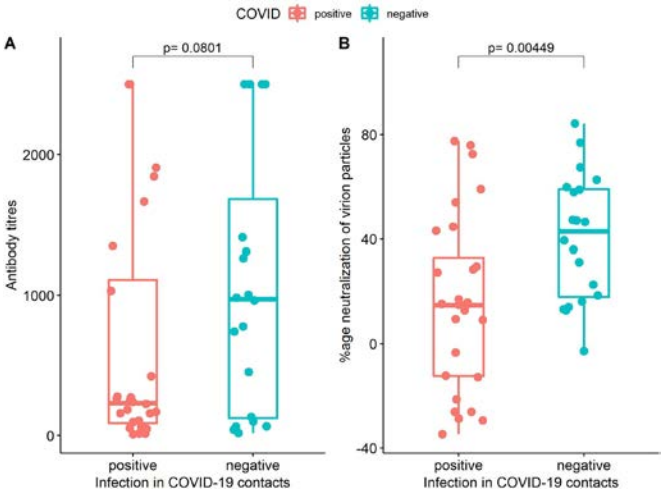

Figure 3 (A) Antibody titres in COVID-19 exposed who had breakthrough infections versus those who did not have. (B) Neutralisation assays in COVID-19 exposed who had breakthrough infections versus those who did not have.

Our study has some limitations. We have assessed antibody levels at only a single time point (4–6 weeks after the second dose). Thus, we are unable to comment on how the rate of change in antibody titres may influence SARS-CoV-2 infection risks. Although waning of immunity may be a risk factor for breakthrough infection after 6 months of the second dose, it is unlikely to have contributed to the breakthrough infections in our cohort as mean follow-up was less than 6 months. Second, we have not analysed the effects of disease activity scores on breakthrough infections due to heterogeneity between the different diseases and drugs used. Underlying immune deregulation and immunosuppressant use can undermine the vaccine efficacy leading to higher breakthrough infections compared with healthy controls.[23] And lastly, our cohort is different from other previously described cohorts in the DMARD usage. The majority of the patients were on MTX or HCQ while those on tofacitinib or biologicals were less than 10%. Due to lower numbers in these sub-groups, they might not have reached statistical significance when their association with vaccination response was compared.[3 5 24 25]

In conclusion, antibody titres appear to predict susceptibility to breakthrough infections, and the absence of an antibody response is the strongest predictor of breakthrough infection on multivariate analysis. This should propel us to explore the routine use of post-vaccination antibody titres as a biomarker. Patients with inadequate humoral response to two doses of vaccines can be prioritised for a booster dose.

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Contributors PS, VS and SAh designed the study . Patient enrolment and data collection was done by PS,AP, SC, SAn, SJ, VS and KKN. Manuscript was draft by SAn and PM. PS accepts full responsibility for the work and/or the conduct of the study, had access to the data and controlled the decision to publish.

Competing interests SA has received honorarium as speaker from Pfizer, DrReddy's, Cipla and Novartis (unrelated to the current work). The other authors declare no conflicts of interest.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval The study was approved by the Ethics Committee of Sree Sudheendra Medical mission (IEC/2021/35) and written informed consent of all the participants was taken.

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EPIDEMIOLOGICAL SCIENCE

Efficacy of COVID-19 vaccines in patients taking immunosuppressants

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ABSTRACT

Objectives We intended to assess the effectiveness of all three US Food and Drug Administration approved COVID-19 vaccines at preventing SARS-CoV-2 infection and COVID-19 hospitalisation in a large cohort of individuals on immunosuppressants for a diverse range of conditions.

Methods We studied the effectiveness of BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna) and Ad26.COV2.S (Johnson & Johnson–Janssen) vaccines among individuals who take immunosuppressants (including disease-modifying antirheumatic drugs and glucocorticoids) by comparing vaccinated (n=97688) and unvaccinated (n=42094) individuals in the Michigan Medicine healthcare system from 1 January to 7 December 2021, using Cox proportional hazards modelling with time-varying covariates.

Results Among vaccinated and unvaccinated individuals, taking immunosuppressants increased the risk of SARS-CoV-2 infection (adjusted HR (aHR)=2.17, 95% CI 1.69 to 2.79 for fully vaccinated and aHR=1.40, 95% CI 1.07 to 1.83 for unvaccinated). Among individuals taking immunosuppressants, we found: (1) vaccination reduced the risk of SARS-CoV-2 infection (aHR=0.55, 95% CI 0.39 to 0.78); (2) the BNT162b2 and mRNA-1273 vaccines were highly effective at reducing the risk of SARS-CoV-2 infection (n=2046, aHR=0.59, 95% CI 0.38 to 0.91 for BNT162b2; n=2064, aHR=0.52, 95% CI 0.33 to 0.82 for mRNA-1273); (3) with a smaller sample size (n=173), Ad26.COV2.S vaccine protection did not reach statistical significance (aHR=0.34, 95% CI 0.09 to 1.30, p=0.17); and (4) receiving a booster dose reduced the risk of SARS-CoV-2 infection (aHR=0.42, 95% CI 0.24 to 0.76).

Conclusions The mRNA-1273 and BNT162b2 vaccines are effective in individuals who take immunosuppressants. However, individuals who are vaccinated but on immunosuppressants are still at higher risk of SARS-CoV-2 infection and COVID-19 hospitalisation than the broader vaccinated population. Booster doses are effective and crucially important for individuals on immunosuppressants.

Key messages

What is already known about this subject?

⇒ The BNT162b2 vaccine is effective in immunocompromised individuals.

⇒ Immunocompromised individuals who were fully vaccinated are at a higher risk of SARS-CoV-2 infection compared with the wider vaccinated population.

What does this study add?

⇒ The BNT162b2 and mRNA-1273 vaccines are effective in a wide range of individuals who take immunosuppressants, but vaccinated individuals in this group remain at higher risk compared with the wider vaccinated population.

⇒ Booster doses are effective at preventing SARS-CoV-2 infections for individuals who take immunosuppressants.

How might this impact on clinical practice or future developments?

⇒ Patients who take immunosuppressants should become fully vaccinated and get a booster dose to gain protection against SARS-CoV-2 infections.

INTRODUCTION

The BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna) and Ad26.COV2.S (Johnson & Johnson–Janssen) vaccines are currently the only COVID-19 vaccines with emergency use authorisation from the US Food and Drug Administration (FDA) since December, 2020. All three vaccines were found to be safe and effective in clinical trials prior to approval. However, these trials excluded individuals who were immunocompromised.[1–3] Since approval, the vaccines have been highly effective at preventing SARS-CoV-2 infection and severe illness,[4] but there is still limited evidence regarding vaccine effectiveness in immunosuppressed individuals. Studies have shown that COVID-19 vaccines have reduced immunogenicity in immunosuppressed individuals compared with immunocompetent individuals.[5–8] In the limited epidemiological research thus far, the approved vaccines appear to be less effective in immunosuppressed individuals relative to the general population.[9–11] However, these studies were all limited by either small sample size, individuals with a specific condition, a single vaccine or a short study period before the Delta variant became dominant and booster dose approved.

Our objective was to assess the effectiveness of all three FDA-approved COVID-19 vaccines at preventing SARS-CoV-2 infection and hospitalisation in a large cohort of individuals who were taking immunosuppressants (hereafter referred to as 'immunosuppressed individuals') compared with individuals not taking immunosuppressants

(hereafter: 'immunocompetent individuals') for a diverse range of conditions. We reviewed electronic health records (EHRs) at Michigan Medicine from 1 January to 7 December 2021. On 12 August 2021, the CDC recommended a booster dose 28 days following their second dose for immunocompromised of the mRNA-1273 and BNT162b2 vaccines.[12] Thus, our study period covers the Delta variant and provided sufficient follow-up data to study the effect of booster dose of mRNA vaccines for immunosuppressed individuals.

An immunosuppressed individual was defined as anyone taking conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), targeted synthetics DMARDs (tsDMARDs), biological DMARDs (bDMARDs) or glucocorticoids (see online supplemental file for a complete list of medications) within 6 months prior to the baseline date. Immunocompetent individuals were defined as those who did not take any immunosuppressants within 6 months prior to the baseline date. A booster dose for immunosuppressed individuals was defined as a third dose for BNT162b2 and mRNA-1273 recipients or a second dose for Ad26.COV2.S recipients. We made comparisons to evaluate vaccine effectiveness in immunosuppressed subjects. We also compared vaccine effectiveness among different types of immunosuppressants and conducted sensitivity analyses by excluding patients with cancer who might be immunosuppressed due to disease or cancer treatment.

METHODS

Patient selection

Using the Centers for Disease Control and Prevention(CDC) definition, we defined an individual as fully vaccinated 2 weeks after a second dose of the BNT162b2 or mRNA-1273 vaccine or 2 weeks after a single dose of the Ad26.COV2.S vaccine.[13] There were a total of 195581 individuals in the EHR system who had an active primary care physician (UM-PCP) at Michigan Medicine and had been seen at a UM primary care location within the past 18 months. We excluded 41062 individuals who were under 18 years, partially vaccinated, had a prior history of COVID-19 or had received a vaccine not approved in the USA. A total of 154519 individuals were included in the final analysis. Baseline date was defined as the date of full vaccination for vaccinated individuals, and 1 January 2021 for unvaccinated individuals.

Time-to-event outcomes and covariates

The primary outcomes were SARS-CoV-2 infections or COVID-19 hospitalisation from 1 January to 7 December2021. We identified SARS-CoV-2 infection based on laboratory test results and the 10th version International Classification of Diseases (ICD-10) code U07.1. Date of infection was identified using test collection date where possible and diagnosis date where test date was not available. COVID-19 hospitalisation was identified using chart review (n=51) where data were available and using ICD-10 codes (n=171) J12.82, M35.81 and J18 where chart review data were not available. Detailed criteria are provided in online supplemental file 1. Demographics included age, gender and race. Charlson Comorbidity Index (CCI)[14] was calculated from ICD-10 diagnosis codes within 1 year before the baseline date. We did not have sufficient follow-up to assess the effect of a booster dose in the immunocompetent group. Therefore, we censored individuals at the date of receiving a third dose for BNT162b2 and mRNA-1273 recipients or a second dose for Ad26.COV2.S recipients in the analysis including immunocompetent subjects.

Statistical analysis

We assessed the effectiveness of the vaccines by comparing fully vaccinated and unvaccinated individuals within the immunosuppressed and immunocompetent groups, based on two time scales: (1) based on calendar time and (2) based on time from vaccination. We also assessed the effectiveness of a booster dose in immunosuppressed individuals using calendar time.

Calendar date analysis. We used data from 1 April to 7 December to compare vaccine effectiveness and data from 12 August to 7 December to compare effect of booster dose of vaccine. The later start date was necessary to compare vaccine groups in the same time period. The Ad26.COV2.S vaccine was not approved for use until late February, meaning there was an insufficient number of individuals fully vaccinated with Ad26.COV2.S until April. The Kaplan-Meier method was used to estimate cumulative incidence curves for each group. In this analysis, the vaccinated individuals were considered unvaccinated until they received their first dose. A Cox model with a time-varying covariate (ie, full vaccination or booster dose) was used to estimate the effect after controlling for age (under 31, 31–50, 51–64, or over 65 years), gender (male vs female), race (Caucasian, African-American or other/unknown) and CCI (0, 1–2, 3–4, or 5^{+}).

Time-from-vaccination analysis

In this analysis, we used data from 1 January to 7 December 2021, to assess the effectiveness of each vaccine based on time from vaccination. The effectiveness of the vaccine in immunocompetent and immunosuppressed individuals was assessed using time-to-event outcomes, defined as the time from full vaccination to SARS-CoV-2 infection or COVID-19 hospitalisation, analysed separately. The Kaplan-Meier method was used to estimate the cumulative incidence of SARS-CoV-2 infection and hospitalised infection, and the log-rank test was used for comparisons between groups. Multivariable Cox regression models were used to compare groups, adjusting for age, gender, race and CCI. To avoid the complexity of selecting a baseline date for unvaccinated individuals, these individuals were not included in this analysis.

In the Cox analyses, we reported adjusted hazard ratio (aHR), 95% confidence interval (CI) and p value. To quantify the relative difference in risk between vaccines, we also estimated the covariate-adjusted cumulative incidence of SARS-CoV-2 infections in each group to assess the absolute difference in risk between vaccines. Specifically, we created a pseudo-population of identical population characteristics as the study individuals for each group and then averaged the predicted values of cumulative incidence. All statistical analyses were performed using R V.4.0.2 (R Core Team, Vienna).

RESULTS

Patient characteristics

The characteristics of fully vaccinated immunosuppressed individuals (n=4283), unvaccinated immunosuppressed individuals (n=1253), fully vaccinated immunocompetent individuals (n=93,405) and unvaccinated immunocompetent individuals (n=40,841) are shown in table 1. The median age was 59 years for fully vaccinated immunosuppressed individuals, 49 years for unvaccinated immunosuppressed individuals, 52 years for fully vaccinated immunocompetent individuals and 39 years for unvaccinated immunocompetent individuals. The study population was majority female (63.9% and 62.2% in the immunosuppressed group for fully vaccinated and unvaccinated, respectively;

Table 1 Patient characteristics

Characteristic	Fully vaccinated group (case group) n=97 688		Unvaccinated group (control group) n=42 094	
	Immunosuppressed, n=4283 (4.4%)	Immunocompetent, n=93405 (95.6%)	Immunosuppressed, n=1253 (3.0%)	Immunocompetent, n=40841 (97.0%)
Age median (IQR)	59 (46–69)	52 (36 – 65)	49 (35–62)	39 (28–54)
Gender, no. (%)				
Male	1591 (37.1)	39814 (42.6)	474 (37.8)	17 472 (42.8)
Female	2692 (63.9)	53588 (58.0)	779 (62.2)	23 369 (57.2)
Race, no. (%)				
Caucasian	3462 (80.8)	72872 (78.0)	971 (77.5)	29 275 (71.7)
African-American	446 (10.4)	6910 (7.4)	189 (15.1)	5758 (14.1)
Other/unknown	375 (8.8%)	13623 (14.6%)	93 (7.4%)	5808 (14.2%)
Vaccine type, no. (%)				
BNT162b2	2046 (47.8)	53178 (56.9)	N/A	N/A
mRNA-1273	2064 (48.2)	35256 (37.7)	N/A	N/A
Ad26.COV2.S	173 (4.1)	4971 (5.4)	N/A	N/A
SARS-CoV-2 infections, no. (%)	119 (2.8)	1146 (1.3)	85 (6.8)	1470 (3.6)
COVID-19 hospitalisations, no. (%)	15 (0.35)	45 (0.05)	7 (0.56)	155 (0.38)

58% and 57.2% in the immunocompetent group for fully vaccinated and unvaccinated, respectively); and predominantly white (80.8% and 77.5% in the immunosuppressed group for fully vaccinated and unvaccinated, respectively; 78% and 71.7% in the immunosuppressed group for fully vaccinated and unvaccinated, respectively). The gender and race distributions were well balanced among the four groups. In the fully vaccinated group, the distribution of vaccine type was well balanced between immunosuppressant and immunocompetent individuals.

Compare risk of infection between immunosuppressant and immunocompetent individuals

Among fully vaccinated and unvaccinated individuals, immunosuppressed individuals had a higher risk of SARS-CoV-2 infection (p<0.001 by log-rank; figure 1A) compared with immunocompetent individuals. Results remain significant after adjusting for age, gender, race and CCI in vaccinated individuals (aHR=2.17, 95% CI 1.69 to 2.79, p<0.0001) and unvaccinated individuals (aHR=1.40, 95% CI 1.07 to 1.83, p=0.0075). We also found that among fully vaccinated individuals, taking immunosuppressants led to a higher risk of COVID-19 hospitalisation (aHR=4.86, 95% CI 2.24 to 10.56, p<0.0001).

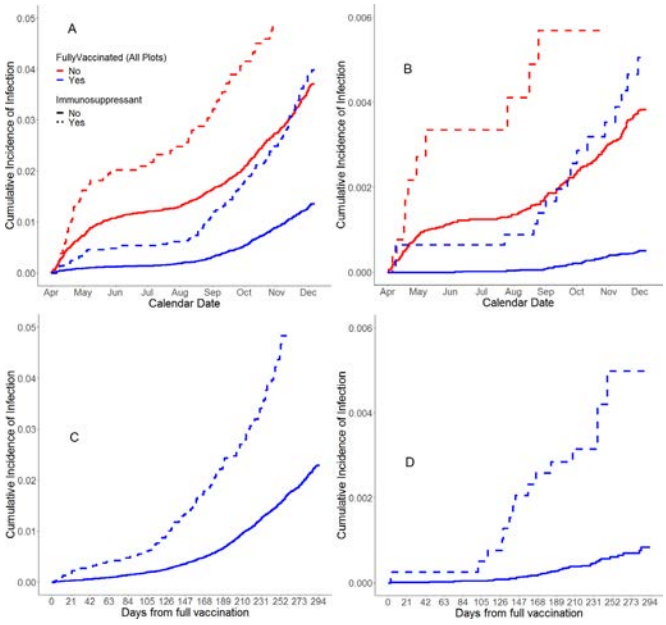

Figure 1 Unadjusted cumulative incidence curves of SARS-CoV-2 infection (A) and COVID-19 hospitalisation (B) based on calendar time. Unadjusted CI curves of SARS-CoV-2 infection (C) and COVID-19 hospitalisation (D) based on vaccination time.

Vaccine effectiveness in immunosuppressed individuals

Based on the calendar time analysis, fully vaccinated immunosuppressed individuals had a lower incidence of SARS-CoV-2 infection and COVID-19 hospitalisation compared with unvaccinated immunosuppressed individuals (p<0.001 by log-rank; figure 1A,B). The result remained the same for the immunocompetent individuals. Vaccination reduced risk of infection in immunosuppressed individuals based on multivariable Cox regression adjusted for age, gender, race and CCI (aHR=0.55, 95% CI 0.39 to 0.78, p<0.0001). The result remained the same for the immunocompetent individuals (aHR=0.35, 95% CI 0.32 to 0.39, p<0.0001; table 2). Full vaccination was associated with lower risk for COVID-19 hospitalisation for immunocompetent individuals (aHR=0.11, 95% CI 0.07 to 0.16, p<0.0001), but it did not reach statistical significance for immunosuppressed individuals, which is likely due to low power (only 15 had COVID-19 hospitalisation among them). We estimated the covariate-adjusted cumulative incidence of SARS-CoV-2 infections per 100000 for April–June, July–September and October–December to be 1423, 1366 and 2753 for unvaccinated immunosuppressed individuals; 1020, 979 and 1978 for unvaccinated immunocompetent individuals; 785, 753 and 1525 for the fully vaccinated immunosuppressed individuals; and 362, 348 and 705 for the fully vaccinated immunocompetent individuals, respectively.

Based on the days-from-vaccination analysis, immunosuppressed individuals had a higher incidence of SARS-CoV-2 infection and COVID-19 hospitalisation compared with immunocompetent individuals (p<0.001 by log-rank; figure 1C,D). The immunosuppressed individuals remained at a higher risk of SARS-CoV-2 infection (aHR=2.41, 95% CI 1.98 to 2.92, p<0.0001) and COVID-19 hospitalisation (aHR=3.47, 95% CI 1.89 to 6.37, p<0.0001) in multivariable Cox regression adjusted for age, gender, race and CCI. We estimated the covariate-adjusted cumulative incidence of SARS-CoV-2

Table 2 Multivariable Cox regression for comparing immunosuppressed versus immunocompetent group based on calendar time

	SARS-CoV-2 infections		COVID-19 hospitalisation	
Variable	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Unvaccinated (immunosuppressed vs immunocompetent)	1.398 (1.068 to 1.829)	0.0075	0.951 (0.435 to 2.080)	0.9984
Fully vaccinated (immunosuppressed vs immunocompetent)	2.173 (1.690 to 2.794)	<0.0001	4.861 (2.238 to 10.56)	<0.0001
Immunocompetent (fully vaccinated vs unvaccinated)	0.354 (0.319 to 0.392)	<0.0001	0.105 (0.067 to 0.162)	<0.0001
Immunosuppressed (fully vaccinated vs unvaccinated)	0.550 (0.387 to 0.781)	0.0001	0.534 (0.196 to 1.452)	0.3724
Age (years)				
Under 31	Ref	Ref	Ref	Ref
31–50	1.497 (1.351 to 1.659)	<0.0001	1.560 (0.970 to 2.509)	0.0668
51–64	1.481 (1.324 to 1.657)	<0.0001	3.119 (1.961 to 4.961)	<0.0001
Over 65	1.243 (1.096 to 1.411)	0.0007	4.550 (2.829 to 7.320)	<0.0001
Gender				
Female	Ref	Ref	Ref	Ref
Male	0.864 (0.804 to 0.929)	<0.0001	1.419 (1.109 to 1.816)	0.0054
Race				
Caucasian	Ref	Ref	Ref	Ref
African-American	0.867 (0.774 to 0.972)	0.0147	1.408 (0.995 to 1.991)	0.0531
Other/unknown	0.548 (0.481 to 0.624)	<0.0001	0.875 (0.570 to 1.341)	0.5397
Charlson Comorbidity Index				
>=5	Ref	Ref	Ref	Ref
3–4	0.876 (0.712 to 1.078)	0.2118	0.478 (0.290 to 0.791)	0.0040
1–2	0.699 (0.587 to 0.832)	<0.0001	0.433 (0.293 to 0.640)	<0.0001
0	0.468 (0.396 to 0.554)	<0.0001	0.187 (0.126 to 0.276)	<0.0001

infections per 100000 for 3 months, 6 months and 9 months after full vaccination to be 362, 1438 and 4396 for immunosuppressed individuals; and 151, 601 and 1855 for immunocompetent individuals, respectively.

Vaccine effectiveness by vaccine type in immunosuppressed individuals

In the analysis compared the three vaccines with unvaccinated controls, we found that all three vaccines were highly effective at preventing SARS-CoV-2 infection and COVID-19 hospitalisation for immunocompetent individuals. For immunosuppressed individuals, there was a significantly lower risk of SARS-CoV-2 infection compared with unvaccinated control for BNT162b2 recipients (aHR=0.59, 95% CI 0.38 to 0.91, p=0.0098; figure 2) and mRNA-1273 recipients (aHR=0.52, 95% CI 0.33 to 0.82, p=0.0015), but we did not find statistically significant vaccine protection for the much smaller sample of Ad26.COV2.S recipients (aHR=0.34, 95% CI 0.09 to 1.30, p=0.17). It is likely that this effect did not reach statistical significance due to low power. Given the estimated HR of 0.35 and current sample size, we found that the power is only 35% at a 0.05 significance level, using a two-sided test based on Cox proportional hazards regression. Because of the small sample size and number of events, there was insufficient statistical certainty when comparing vaccine effectiveness against COVID-19 hospitalisations for immunosuppressed individuals.

Effectiveness of booster dose in immunosuppressed individuals

Figure 1A shows that the incidence of SARS-CoV-2 infection increased dramatically for fully vaccinated immunosuppressed individuals after late August and that their cumulative incidence increased over the unvaccinated immunocompetent individuals by late November, suggesting their immunity waned faster than the general population. In this analysis, individuals were censored at the date of receiving a booster dose; therefore, we conducted a further analysis to study the effectiveness of the booster dose in immunosuppressed individuals.

We compared individuals who had a booster dose (n=1650, 38.5%) versus individuals before taking or who did not take the booster dose (n=2633, 61.5%). We found that fully vaccinated immunosuppressed individuals who had a booster dose had a lower incidence of SARS-CoV-2 infection compared with fully vaccinated immunosuppressed individuals who did not (p<0.001 by log-rank; figure 3). This result remained significant in multivariable Cox regression after adjusting for age, gender, race and CCI (aHR=0.42, 95% CI 0.24 to 0.76, p=0.0037).

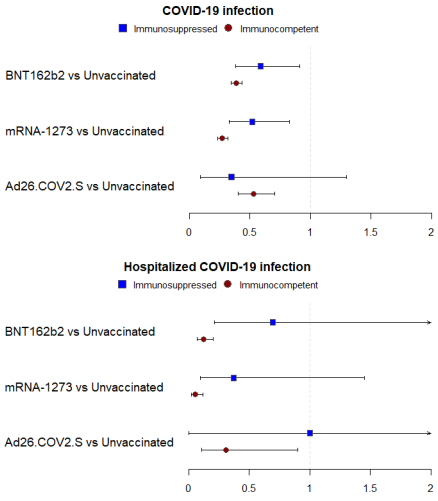

Figure 2 HRs for SARS-CoV-2 infection and COVID-19 hospitalisation for each vaccine group compared with the unvaccinated group among immunosuppressed and immunocompetent individuals. Comparisons using multivariable COX model adjusting for age, gender, race and CCI. CCI, Charlson Comorbidity Index.

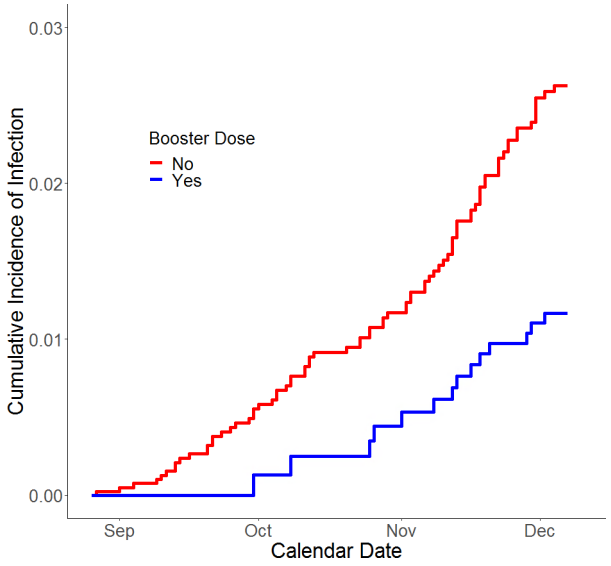

Figure 3 Unadjusted CI curves of SARS-CoV-2 infection in immunosuppressed individuals who took a booster dose or not based on calendar time.

Sensitivity analysis

We studied a comprehensive list of immunosuppressant drugs used to treat patients with autoimmune disease or who had transplantation. However, individuals who did not take these medications might also be in an immunosuppressive condition, for instance, cancer individuals who were immunosuppressed due to the disease or taking immunosuppressive cancer therapy. In addition, transplant patients may have lower exposure to SARS-CoV-2 infection due to shielding or risk avoidant behaviour. Thus, we conducted sensitivity analyses by excluding patients who had these conditions.

We first excluded patients who had a history of cancer, who were identified from the ICD-10 diagnosis codes in the 1 year before the baseline date (n=750 (13.6%) immunosuppressed and n=207 (3.9%) immunocompetent). We further excluded patients who had a transplant (n=550 (9.9%) immunosuppressed and n=500 (0.4%) immunocompetent) and performed the same analyses again. Conclusions remained the same on vaccine effectiveness and comparisons between immunosuppressed and immunocompetent individuals based on the two time scales (data not shown).

Vaccine effectiveness by immunosuppressant type

Among the 4283 fully vaccinated immunosuppressed individuals, there were 674 (15.7%) individuals who were only treated with csDMARDs, 265 (6.2%) individuals who were only treated with bDMARDs (combined tsDMARDs and bDMARDs), 210 (4.9%) individuals who were treated with both csDMARDs and bDMARDs and 1528 (35.7%) individuals who were only treated with glucocorticoids. We excluded the individuals who were treated with both DMARDs and glucocorticoids (1606, 37.5%). Based on the calendar time analysis and time-from-vaccination analysis, we found no significant differences in SARS-CoV-2 infection between these types of immunosuppressants (online supplemental figure).

DISCUSSION

We found that immunosuppressed individuals who had received one of the three approved COVID-19 vaccines were at substantially lower risk of SARS-CoV-2 infection compared with those who were unvaccinated. Specifically, we found that BNT162b2 and mRNA-1273 vaccines were highly effective at preventing SARS-CoV-2 infection in immunosuppressed individuals. However, due to the small sample size, the statistical power to detect the effectiveness of the Ad26.COV2.S vaccine was only 35%; if the sample size was increased by 10 times (close to the same size for BNT162b2 or mRNA-1273), the power would be over 95%. Overall, these results are highly reassuring, given concerns that reduced immune response would lead to lower vaccine effectiveness in immunosuppressed individuals and the lack of data from the clinical trials conducted prior to vaccine approval. We also found that booster doses were highly effective at reducing risk of infection and hospitalisation within this group. Giving a booster dose to immunosuppressed individuals who have not yet received one is crucially important.

We also observed an increase in incidence of infection among all individuals after 1 July, once the Delta variant became the dominant variant in the USA (see figure 1A). This increase appears to be larger for vaccinated immunosuppressed individuals compared with other vaccinated individuals. Based on the analysis using time from vaccination (see figure 1C comparing immunocompetent and immunosuppressed individuals who are vaccinated), this could be explained by vaccine-induced immunity waning more quickly for immunosuppressed individuals. It is also possible that the Delta variant affected vaccine-induced immunity differently for immunosuppressed compared with immunocompetent individuals. Regardless of the explanation, this underlines the importance of immunosuppressed individuals receiving booster shots, as their immunity due to vaccination appears to be reduced later in the study period and is likely to wane further in the coming months. It also indicates that public health officials should expect that the immunity conferred by booster shots will wane more quickly for immunosuppressed individuals and incorporate this into decision making regarding approval of additional booster doses in the future.

In late December 2021, the Omicron variant rapidly increased in prevalence and now accounts for a majority of new SARS-CoV-2 infections. Although this study did not cover Omicron infections, the conclusions for immunosuppressed individuals are likely to remain the same. Vaccines will offer protection, but lower immunity after vaccination and rapidly waning immunity will put them at higher risk of SARS-CoV-2 infection and COVID-19 hospitalisation compared with immunocompetent individuals.

Limitations of this study include having data from a single health institution and underestimation of SARS-CoV-2 infection due to limitations in testing and reporting of tests received at outside sites. EHR data have limitations such as inaccuracy and missingness. Our determination of disease (such as cancer and transplantation) and calculation of comorbidity scores relied on ICD-10 codes, which may prone to errors.[15] CCI, which we used to capture comorbidities, is not necessarily a comprehensive metric for determining patient health and may miss some prognostic factors for SARS-CoV-2 infection. Despite this limitation, the CCI is more accurate than using individual ICD-10 codes.[16]

Immunosuppressed subjects might interact more with the health system compared with immunocompetent subjects due to treatment of their underlying condition and vulnerability to other health problems, leading to more complete infection data for this group. To reduce the bias caused by this issue, we defined the study cohort to individuals who had an active primary care physician at the University of Michigan.

Furthermore, immunosuppressants are prescribed for a wide variety of medical conditions such as autoimmune diseases,

pulmonary fibrosis, gastrointestinal or endocrine disorders. As a result, the degree of immunosuppression and medical vulnerability is not homogenous across all immunosuppressed patients. We conducted sensitivity analyses by excluding certain conditions or procedures, such as cancer and transplantation, but cannot fully determine whether higher infection rates for immunosuppressed individuals are due to immunosuppressant medications or the underlying conditions they are used to treat.

Despite these limitations, our results provide important information on vaccines effectiveness in immunosuppressed individuals. Vaccines are highly effective at preventing SARS-CoV-2 infections in this group, despite reduced effectiveness relative to the broader population. It is crucial that immunosuppressed individuals take boosters as soon as possible as they remain at elevated risk of SARS-CoV-2 infection and COVID-19 hospitalisation than other vaccinated individuals.

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CLINICAL SCIENCE

Pausing methotrexate improves immunogenicity of COVID-19 vaccination in elderly patients with rheumatic diseases

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ABSTRACT

Objective To study the effect of methotrexate (MTX) and its discontinuation on the humoral immune response after COVID-19 vaccination in patients with autoimmune rheumatic diseases (AIRD).

Methods In this retrospective study, neutralising SARS-CoV-2 antibodies were measured after second vaccination in 64 patients with AIRD on MTX therapy, 31 of whom temporarily paused medication without a fixed regimen. The control group consisted of 21 patients with AIRD without immunosuppressive medication.

Results Patients on MTX showed a significantly lower mean antibody response compared with patients with AIRD without immunosuppressive therapy (71.8% vs 92.4%, p<0.001). For patients taking MTX, age correlated negatively with immune response (r=−0.49; p<0.001). All nine patients with antibody levels below the cut-off were older than 60 years. Patients who held MTX during at least one vaccination showed significantly higher mean neutralising antibody levels after second vaccination, compared with patients who continued MTX therapy during both vaccinations (83.1% vs 61.2%, p=0.001). This effect was particularly pronounced in patients older than 60 years (80.8% vs 51.9%, p=0.001). The impact of the time period after vaccination was greater than of the time before vaccination with the critical cut-off being 10 days.

Conclusion MTX reduces the immunogenicity of SARS-CoV-2 vaccination in an age-dependent manner. Our data further suggest that holding MTX for at least 10 days after vaccination significantly improves the antibody response in patients over 60 years of age.

Key messages

What is already known about this subject?

⇒ Patients receiving methotrexate (MTX) have a reduced immune response after COVID-19 vaccination and holding MTX has shown to increase the immunogenicity after influenza vaccination.

⇒ Yet, no previous studies have analysed the effect of MTX-hold for COVID-19 vaccination.

What does this study add?

⇒ This study identified old age (≥60 years), short vaccine interval and MTX continuation as critical factors for an inadequate antibody response.

⇒ We found a minimum of 10 days between vaccination and re-intake of MTX as the critical threshold to increase immunogenicity for patients ≥60 years of age.

How might this impact on clinical practise or future developments?

⇒ Regarding ongoing booster vaccinations, our data suggest that especially older patients on MTX should hold MTX for at least 10 days after receiving a COVID-19 vaccination.

INTRODUCTION

Until November 2021, SARS-CoV-2 had infected at least 250 million people worldwide and caused about 5 million deaths in a 23-month period.[1] At the same time, enormous knowledge about SARS-CoV-2 and the related disease COVID-19 have been generated and the possibilities for prevention, diagnostics and treatments have improved remarkably.

Methotrexate (MTX) has been used for decades to treat a wide variety of immune-mediated diseases in oncology, rheumatology, dermatology, gastroenterology and neurology. Following prednisolone, MTX is the most prescribed anti-inflammatory drug worldwide with 1 million patients on MTX in the USA alone.[2]

Various immunosuppressants reduce the immune response after COVID-19 vaccination.[3] Although several research groups have recently described a reduced vaccination response under MTX,[4 5] in some cohorts MTX had no negative influence.[6 7] Most of these studies did not collect data on whether or not patients had paused MTX during vaccinations, although more than one-third of patients had modified their

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medication on their own or on the advice of their rheumatologist, according to a recent survey.[8] The discontinuation of immunosuppressive medication can improve the vaccination response as recently shown for mycophenolate.[9]

A reduced vaccination response under MTX was first described in 2016 for influenza vaccination.[10] Follow-up data showed the increase in humoral immune response when pausing MTX 2 weeks before and after vaccination or only 2 weeks after vaccination.[11 12] The time after and not before vaccination was decisive.[13] However, data regarding MTX-hold during COVID-19 vaccination are still lacking, which is why current guidelines are based on experience with influenza vaccines, not considering mRNA-based technology used for COVID-19 vaccinations. Although current guidelines by the American College of Rheumatology as well as the German Society for Rheumatology recommend holding MTX 1–2 weeks after COVID-19 vaccination,[14 15] the European League Against Rheumatism does not recommend pausing MTX.[16]

Therefore, our main objective was to study the effect of MTX and its discontinuation on the humoral immune response after COVID-19 vaccination in patients with autoimmune rheumatic diseases (AIRD). Secondary objective

Table 1 Characteristics of patients on MTX who held and continued MTX

	MTX continued (n=33)	MTX-hold (n=31)	MTX all (n=64)	P value*
Age, mean (SD)	62.4 (14.2)	59.6 (11.1)	61.1 (12.8)	0.391
Female, n (%)	21 (63.6)	24 (77.4)	45 (70.3)	0.251
BMI, mean (SD)	26.4 (4.52)	24.7 (3.30)	25.6 (4.03)	0.102
Rheumatic diagnosis				0.759
Rheumatoid arthritis, n (%)	21 (63.6)	23 (74.2)	44 (68.8)	
Psoriatic arthritis, n (%)	5 (15.2)	2 (6.5)	7 (10.9)	
Others, n (%)†	7 (21.2)	6 (19.4)	13 (20.3)	
Medication				0.553
MTX-mono, n (%)	14 (42.4)	12 (38.7)	26 (40.6)	
MTX+prednisolone, n (%)	7 (21.2)	5 (16.1)	12 (18.8)	
MTX+anti-TNF-α, n (%)‡	4 (12.1)	7 (22.6)	11 (17.2)	
MTX+anti-TNF-α+prednisolone, n (%)‡	5 (15.2)	2 (6.5)	7 (10.9)	
MTX+others, n (%)§	3 (9.1)	5 (16.1)	8 (12.5)	
Additional prednisolone, n (%)	12 (36.4)	8 (25.8)	20 (31.3)	0.377
Prednisolone dose (mg/day), mean (SD)	3.0 (1.8)	2.6 (1.1)	2.9 (1.6)	0.572
MTX dose (mg/week), mean (SD)	13.2 (4.5)	13.1 (4.1)	13.2 (4.3)	0.973
MTX oral application, n (%)	16 (48.5)	10 (32.3)	26 (40.6)	0.205
Vaccination				0.896
BNT162b2, n (%)	24 (72.7)	23 (74.2)	47 (73.4)	
mRNA-1273, n (%)	5 (15.2)	3 (9.7)	8 (12.5)	
AZD1222, n (%)	3 (9.1)	4 (12.9)	7 (10.9)	
AZD1222+BNT162b2, n (%)	1 (3.0)	1 (3.2)	2 (3.1)	
Vaccine interval in days, mean (SD)	39.0 (14.8)	41.9 (15.3)	40.4 (15.0)	0.444
Immune response				
Days from second vaccination, mean (SD)	35 (23)	28 (22)	32 (22)	0.237
Anti-RBD-IgG (S/CO), mean (SD)	3.7 (3.4)	6.3 (2.6)	5.0 (3.3)	**0.001**
Neutralising capacity (%), mean (SD)	61.2 (30.2)	83.1 (21.2)	71.8 (28.3)	**0.001**
Responders, neutralisation capacity, n (%)¶	25 (75.8)	30 (96.8)	55 (85.9)	**0.017**
Responders, anti-RBD-IgG response, n (%)**	21 (63.6)	30 (96.8)	51 (79.7)	**0.002**
MTX-hold				
For both vaccinations, n (%)	NA	24 (77.4)		
For only the first vaccination, n (%)	NA	2 (6.5)		
For only the second vaccination, n (%)	NA	5 (16.1)		
Duration of MTX-hold for first vaccination (days), mean (SD)	NA	15.1 (6.6)		
Duration of MTX-hold for second vaccination (days), mean (SD)	NA	16.9 (6.6)		

Significant results are in bold.
*P values compare MTX continued and MTX-hold and were calculated using the exact unconditional z-pooled test for binary variables (female, additional prednisolone, MTX oral application, responders neutralisation capacity, responders anti-RBD-IgG response), χ^2 test for categorical variables (rheumatic diagnosis, medication, vaccination) and unpaired t-test with Welch's correction for continuous variables.
†For MTX continued: ANCA-associated vasculitis (n=1), axial spondyloarthritis (n=1), polymyalgia rheumatica (n=2), systemic sclerosis (n=1), myositis (n=1), systemic lupus erythematosus (n=1). For MTX-hold: axial spondyloarthritis (n=1), polymyalgia rheumatica (n=1), primary Sjögren's syndrome (n=1), systemic sclerosis (n=2), myositis (n=1).
‡Adalimumab, certolizumab, etanercept, golimumab, infliximab.
§For MTX continued: hydroxychloroquine (n=1), secukinumab (IL-17 inhibitor, n=1), ustekinumab (IL-12/IL-23 inhibitor, n=1). For MTX-hold: hydroxychloroquine (n=1), leflunomide (n=2), leflunomide+prednisolone (n=1), secukinumab (IL-17 inhibitor, n=1).
¶Defined as neutralising capacity against SARS-CoV-2 ≥30%.
**Defined as anti-RBD-IgG levels >1.0 S/CO.
ANCA, antineutrophil cytoplasmic antibody; BMI, body mass index; IL, interleukin; MTX, methotrexate; NA, not available; S/CO, signal/cut-off; TNF, tumour necrosis factor.

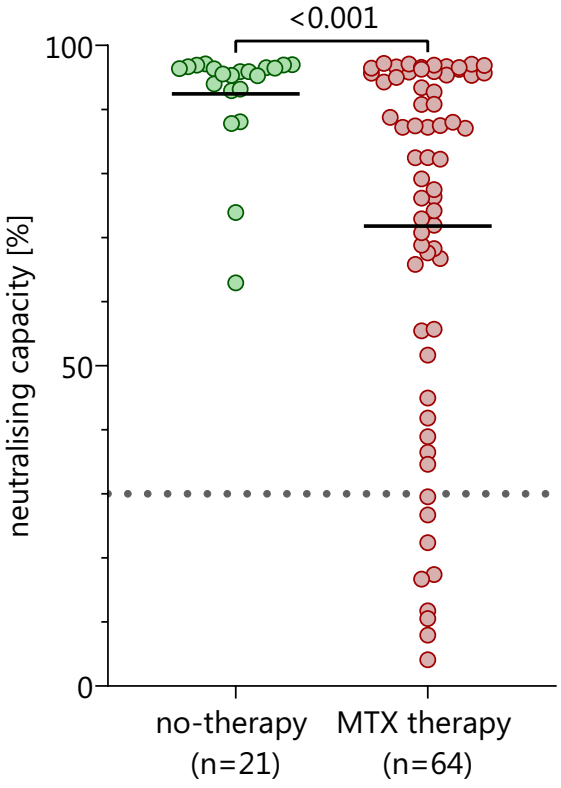

Figure 1 Comparison of neutralising capacity in patients with autoimmune rheumatic diseases (AIRD) without immunosuppression and with methotrexate (MTX) therapy. Neutralising capacity measured using surrogate virus neutralisation test after second vaccination in patients on MTX (n=64) represented by red dots versus patients with AIRD who were under no immunosuppressive therapy during both vaccinations (n=21) represented by green dots. P values were calculated using the parametric unpaired t-test with Welch's correction.

was to determine additional influencing factors on antibody response in these patients.

METHODS

Study design and participants

This is a retrospective subanalysis of the VACCIMMUN study, which is an observational cohort study among patients with AIRD at the Charité Department for Rheumatology and Clinical Immunology in Berlin, Germany. Participants were recruited between April and September 2021 and had to meet the following inclusion criteria: age 18 years or older, AIRD diagnosis and vaccination with a COVID-19 vaccine authorised for use in Germany. For this analysis, only patients with AIRD under MTX therapy were considered, receiving either only MTX or MTX combined with low-dose prednisolone (defined as ≤5 mg/day), tumour necrosis factor-α inhibitors, hydroxychloroquine, leflunomide, interleukin (IL)-17 or IL-12/IL-23 inhibitors, since these immunosuppressive comedications are not known to have a remarkable impact on the immune response after vaccination.[15] Additionally, patients with AIRD who were vaccinated under no immunosuppressive therapy served as controls. Information regarding medical history including COVID-19 vaccination status and immunosuppressive therapy were provided directly by patients and additionally validated with medical records. At the time of blood drawing, patients were asked about their MTX intake schedule around vaccinations. The decision on continuing or holding MTX was made by the patient or the attending physician and was only observed in the study. Patients who reported to have changed their MTX-intake schedule resulting in an MTX interval longer than 7 days around first or second vaccination were compared with patients who continued MTX therapy throughout both vaccinations.

Laboratory analyses

Antibody response was measured predominantly about 2 weeks after the second dose of vaccination with maximum range from 11 to 112 days. Neutralising antibody levels were assessed using a surrogate virus neutralisation test (cPass Neutralisation, Medac, Wedel, Germany).[17] Following the manufacturer's protocol, patients who reached inhibition rates ≥30% were considered to have demonstrated a SARS-CoV-2-specific humoral response and are further defined as responders, while patients with inhibition rates <30% are defined as non-responders. Additionally, IgG antibodies against nucleocapsid, receptor binding domain (RBD), full spike and the S1 domain of the spike protein were tested using SeraSpot anti-SARS-CoV-2 IgG microarray-based immunoassay (Seramun Diagnostica, Heidesee, Germany) and served here for further validation purposes. Hence, all calculations were additionally performed using anti-RBD-IgG levels and can be found in the supplements. The threshold for reactivity for anti-SARS-CoV-2 IgG levels was set at >1.00 signal/cut-off in accordance with manufacturer's protocol.

Statistical analysis

Descriptive statistics included mean with SD and absolute and relative frequencies. The exact unconditional z-pooled test[18] and χ^2 test were applied for binary and categorical data and the unpaired t-test with Welch's correction for continuously distributed variables to perform hypotheses tests for group differences, as appropriate. The likelihood of response to vaccination was modelled by a Poisson generalised linear model with robust error variances and log link function including the covariates age, gender, MTX monotherapy, MTX in combination with prednisolone, MTX in combination with other disease-modifying antirheumatic drugs (DMARDs)±prednisolone, MTX-hold and vaccine interval as suggested by Zou.[19] These covariates were selected based on the theoretical assumption that they could affect vaccination success and on the results of the univariate analysis. The association between antibody results (dependent variables anti-RBD-IgG concentrations or neutralising capacity) and the covariates age, gender, MTX monotherapy, MTX in combination with prednisolone and MTX in combination with other DMARDs±prednisolone, MTX-hold, vaccine interval and timing and duration of MTX-hold was estimated by a linear regression model. The unstandardised and standardised beta-coefficients were calculated for linear regression analyses in order to compare the strengths of association between parameters. The area under the curve (AUC) was calculated after fitting a logistic regression model to provide a measure of strengths of association for dichotomous outcomes. The Youden index was used to estimate thresholds for age and time of MTX break before and after vaccination from receiver operating characteristics (ROC). Statistical analyses were performed using GraphPad Prism V.9.2.0, R V.4.1.2 and STATA V.12.1.

Table 2 Comparison of vaccination responders and non-responders among patients with AIRD taking MTX

	Responders* (n=55)	Non-responders (n=9)	P value†
Age, mean (SD)	59.5 (12.9)	70.3 (6.67)	**0.001**
Female, n (%)	42 (76.4)	3 (33.3)	**0.010**
BMI, mean (SD)	25.4 (4.09)	26.6 (3.70)	0.389
Medication			0.616
MTX-mono, n (%)	23 (41.8)	3 (33.3)	
MTX+prednisolone, n (%)	8 (14.5)	4 (44.4)	
MTX+anti-TNF-α, n (%)‡	10 (18.2)	1 (11.1)	
MTX+anti-TNF-α+prednisolone, n (%)‡	6 (10.9)	1 (11.1)	
MTX+HCQ, n (%)	2 (3.6)	0	
MTX+leflunomide, n (%)§	3 (5.5)	0	
MTX+anti-IL-17, n (%)¶	2 (3.6)	0	
MTX+anti-IL-12/IL-23, n (%)**	1 (1.8)	0	
MTX dose (mg/week), mean (SD)	13.0 (4.29)	14.2 (4.33)	0.469
MTX oral application, n (%)	25 (45.5)	1 (11.1)	0.057
Additional prednisolone, n (%)	15 (27.3)	5 (55.6)	0.103
Prednisolone dose (mg/day), mean (SD)	2.5 (1.4)	3.8 (1.6)	0.174
Vaccination			0.609
BNT162b2, n (%)	39 (70.9)	8 (88.9)	
mRNA-1273, n (%)	7 (12.7)	1 (11.1)	
AZD1222, n (%)	7 (12.7)	0	
AZD1222+BNT162b2, n (%)	2 (3.6)	0	
Vaccine interval in days, mean (SD)	42 (15)	31 (9)	**0.011**
Days from second vaccination, mean (SD)	30 (22)	40 (22)	0.259
MTX-hold, n (%)	30 (54.5)	1 (11.1)	**0.017**
For both vaccinations, n	23 (41.8)	1 (11.1)	
For only the first vaccination, n	2 (3.6)	0	
For only the second vaccination, n	5 (9.0)	0	

*Defined by neutralising capacity against SARS-CoV-2 ≥30%.
†P values were calculated using the exact unconditional z-pooled test for binary variables (female, MTX oral application, additional prednisolone, MTX-hold), χ^2 test for categorical variables (medication, vaccination) and unpaired t-test with Welch's correction for continuous variables.
‡Adalimumab, certolizumab, etanercept, golimumab, infliximab.
§Additional low-dose prednisolone for n=1.
¶Secukinumab.
**Ustekinumab.
AIRD, autoimmune rheumatic diseases; BMI, body mass index; HCQ, hydroxychloroquine; IL, interleukin; MTX, methotrexate; TNF, tumour necrosis factor.

Patient and public involvement

This study aimed to provide evidence for future recommendations due to questions asked regarding MTX intake by patients and physicians. However, patients and the public were not directly involved in process of designing.

RESULTS

Patient characteristics

Of 73 eligible patients receiving MTX, 9 were excluded due to unacceptable immunosuppressive comedication, irregular medication regimens and unclassifiable MTX-hold. The final cohort consisted of 64 patients with AIRD taking MTX (mean age 61 years, 70.3% women) and 21 patients with AIRD who did not receive any kind of immunosuppressive therapy as a control group (mean age 61, 90.5% women). Detailed clinical characterisation is given in online supplemental table 1. Patients in the no-therapy group were of similar age and body mass index (BMI), but more often female. They were less often diagnosed with rheumatoid arthritis and more often with systemic sclerosis.

Of 64 patients on MTX, 31 patients reported to have held MTX for at least one vaccination (MTX-hold) while 33 patients had continued their MTX therapy without any interruption (MTX continued, table 1). Blood sampling occurred slightly earlier in the MTX-hold group than in the MTX continued group. There were no significant differences between these two groups regarding age, BMI, distribution of sex, vaccination regimes, diagnoses and immunosuppressive comedications (table 1).

MTX reduces vaccination response

Patients with AIRD without immunosuppressive therapy showed a significantly higher neutralising capacity (mean 92.4%, SD: 8.6) than patients with AIRD taking MTX (mean 71.8%, SD: 28.3, p<0.001, figure 1, online supplemental figure 1 for anti-RBD-IgG). This was still the case after adjusting for the possible confounders gender, age, vaccine regime and vaccine interval, AIRD diagnosis and duration from second vaccination to blood draw in a logistic regression (for neutralising capacity: beta=−19.5, 95% CI −31.4 to −7.7, p=0.002; for anti-RBD-IgG: beta=−1.61, 95% CI −3.03 to −0.18, p=0.028). None of the patients without immunosuppressive therapy were classified as non-responders (defined by neutralisation activity <30%), compared with 14.1% (n=9) among patients on MTX. Taking patients without immunosuppressive therapy in

Table 3 Association of neutralising capacity and anti-RBD-IgG concentration with selected covariates in univariate and multivariable analyses (n=64)

	Univariate analysis				Multivariable analysis		
	RR*	P value	95% CI	AUC	RR*	P value	95% CI
Outcome: anti-RBD-IgG concentration >1 S/CO							
Female	1.18	0.280	0.88 to 1.58	0.60	1.23	0.125	0.94 to 1.62
Age (years)†	**0.93**	**<0.001**	**0.89 to 0.97**	**0.89**	**0.94**	**0.001**	**0.90 to 0.97**
MTX monotherapy	1.00			0.63	1.00		
MTX+prednisolone	0.79	0.284	0.51 to 1.22		0.86	0.415	0.60 to 1.24
MTX combination±prednisolone	1.05	0.687	0.84 to 1.30		1.04	0.693	0.86 to 1.25
MTX dose (mg)	0.99	0.688	0.97 to 1.02	0.54			
MTX-hold	**1.39**	**0.006**	**1.10 to 1.76**	**0.74**	**1.27**	**0.020**	**1.04 to 1.56**
Vaccine interval	**1.006**	**0.016**	**1.001 to 1.010**	**0.75**	**1.004**	**0.024**	**1.0006 to 1.008**
Outcome: neutralisation capacity ≥30%							
Female	1.36	0.055	0.99 to 1.87	0.72	**1.43**	**0.012**	**1.08 to 1.90**
Age (years)†	**0.96**	**0.008**	**0.92 to 0.99**	**0.77**	**0.96**	**0.018**	**0.93 to 0.99**
MTX monotherapy	1.00			0.68	1.00		
MTX+prednisolone	0.75	0.194	0.49 to 1.15		0.75	0.099	0.53 to 1.06
MTX combination±prednisolone	1.04	0.641	0.87 to 1.25		0.98	0.838	0.84 to 1.15
MTX dose (mg)	0.99	0.452	0.97 to 1.01	0.58			
MTX-hold	**1.28**	**0.019**	**1.04 to 1.57**	**0.72**	**1.17**	**0.039**	**1.00 to 1.38**
Vaccine interval	1.002	0.235	0.999 to 1.006	0.63	1.001	0.423	0.998 to 1.004

*RR was estimated by a Poisson generalised linear model with robust error variances and log link function in univariate and multivariable analyses according to Zou.[19]
†RR for increase by 5 years.
AUC, area under the curve; MTX, methotrexate; RR, relative risk; S/CO, signal/cut-off.

our cohort as a reference group for a typical antibody response after vaccination, the threshold for a not-altered inhibition rate could be set at 87.6% (AUC 0.75, Youden index 49.9). Accordingly, 38 of 64 patients on MTX (59.4%) demonstrated a lower antibody response after two vaccinations compared with an untreated group of patients with AIRD.

Factors influencing antibody response in patients on MTX

To identify factors influencing the antibody response under MTX, we compared COVID-19 vaccination responders (n=55, 85.9%) and non-responders (n=9, 14.1%) defined by neutralisation activity. Both groups were comparable in BMI, vaccine type, MTX application form, additional prednisolone intake, time of blood draw and immunosuppressive comedication (table 2). Dosage of MTX was not significantly associated with vaccination success (Spearman's rank correlation, r=−0.02, p=0.867). However, a higher neutralisation capacity was significantly associated with young age, MTX-hold and female gender in univariate analysis (table 2) and multivariable analysis (table 3). If classification into responders and non-responders was based on anti-RBD-IgG results, 13 patients would fall into the non-responder group. While the effects of age and MTX-hold were still significant using anti-RBD-IgG levels, this was not the case for gender (online supplemental table 2, table 3). A longer vaccine interval was associated with an adequate humoral response to vaccination in our cohort (significant in t-test for neutralising capacity and anti-RBD-IgG levels; only significant in multivariable analysis for anti-RBD-IgG levels). In the following, we will analyse the effect of age and MTX-hold in more detail.

Effect of MTX-hold and age

Patients who had changed their MTX intake schedule for at least one vaccination showed a significantly higher antibody response than patients who continued their MTX intake (p=0.001, figure 2A, online supplemental figure 2A for anti-RBD-IgG). Mean neutralisation was 61.2% for patients who continued their therapy and 83.1% for patients who held MTX (table 1). There was only one non-responder (3.2%) in the MTX-hold group, while there were eight non-responders (24.2%) in the MTX continued group. The effect of pause persisted in patients with MTX monotherapy, indicating that this effect cannot be explained by the existing comedication (online supplemental figure 3).

Vaccination response correlated significantly with age (Spearman's rank correlation, −0.49, p<0.001, figure 3, online supplemental figure 4 for anti-RBD-IgG). No patient younger than 60 years was classified a non-responder which is why we further distinguished the MTX-hold and continued groups into patients older and younger than 60 years of age (figure 2B, online supplemental figure 2B for anti-RBD-IgG). Considering only patients who continued their MTX intake, patients ≥60 years of age (mean 51.9%) had a 30.7 percentage points lower mean inhibition rate than patients <60 years (mean 82.6%). Vice versa, neutralisation levels were 28.9 percentage points higher in patients older than 60 years who held MTX (mean 80.8%) compared with those who continued MTX (mean 51.9%). In contrast, when regarding patients under 60 years there were no significant differences in neutralisation rates between patients who held or continued MTX therapy.

Effect of timing and duration of MTX-hold

In the following, we considered all 64 patients and analysed the MTX interval at the time of vaccination, which was defined by the time between last MTX intake and vaccination (time before vaccination=T_{BV}) and the time between vaccination and re-intake of MTX (time after vaccination=T_{AV}, figure 4). One patient could not recall on which day MTX was taken and was therefore not considered for calculations of T_{BV} and T_{AV}. We found that the duration of the MTX interval ($T_{BV}+T_{AV}$) significantly correlates with

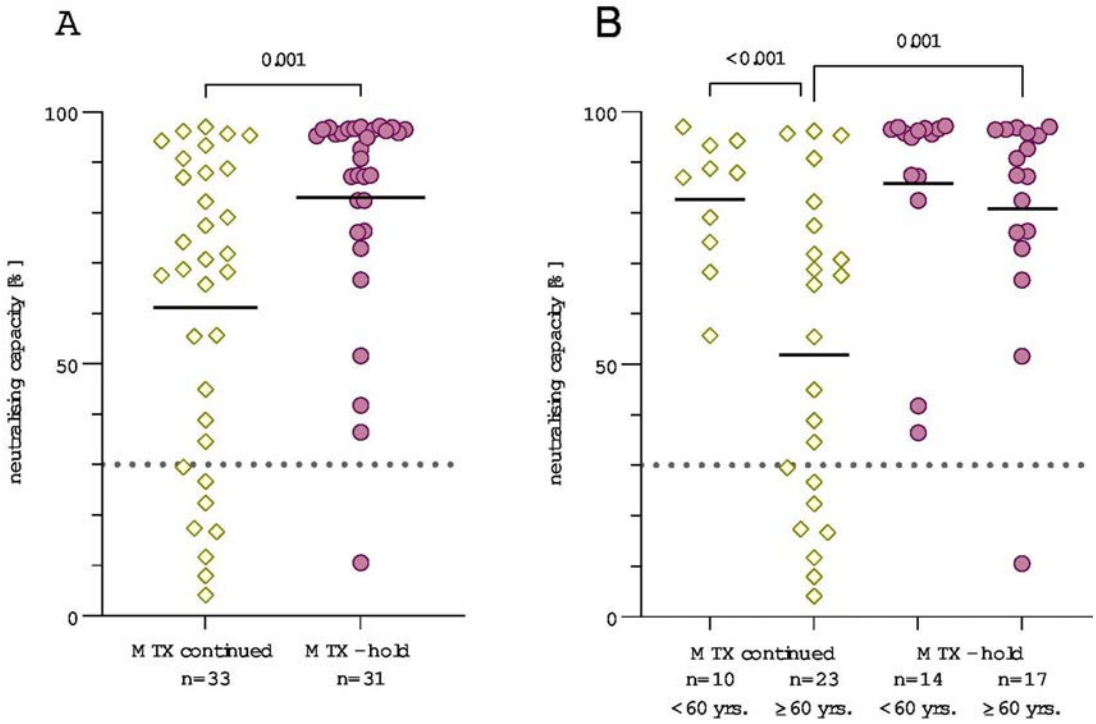

Figure 2 Comparison of patients with autoimmune rheumatic diseases (AIRD) who continued or held their methotrexate (MTX) during the COVID-19 vaccination. (A) Neutralising capacity measured using surrogate virus neutralisation test compared between patients who held MTX during vaccination (n=31) and patients who continued MTX therapy (n=33). (B) Neutralising capacity differentiated by age groups <60 years and ≥60 years. P values were calculated using the parametric unpaired t-test with Welch's correction. Dotted line marks the cut-off value following manufacturer's protocol (≥30%). Yellow squares represent patients who continued MTX therapy, purple dots represent patients who held MTX for at least one vaccination.

neutralising capacity (Spearman's rank correlation, r=0.47, p<0.001). We further analysed which of these time periods is most likely to determine antibody response. By using linear regression analysis, we found time after vaccination (T_{AV}) to be highly significant for adequate neutralisation rate and anti-RBD-IgG concentration in the elderly, but not for younger patients (table 4). Here, 10 days between vaccination and MTX re-intake (T_{AV}) were determined as the critical cut-off based on the Youden index from ROC curve.

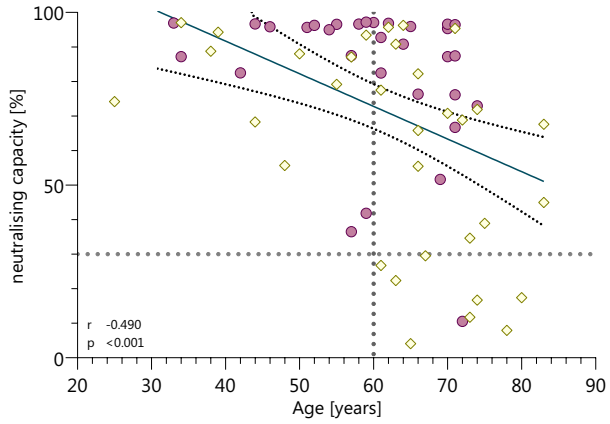

Figure 3 Correlation of age and neutralising capacity measured using surrogate virus neutralisation test. Purple dots represent patients who held methotrexate (MTX) during vaccination (n=31), yellow squares represent patients who continued MTX therapy (n=33). Neutralising antibodies were measured using a surrogate virus neutralisation test. Dotted lines mark the cut-off value following manufacturer's protocol (≥30%) and the cut-off age used for further analysis at 60 years. P value and correlation coefficient were calculated using the Spearman's rank correlation.

DISCUSSION

Our study found a reduced COVID-19 vaccination response in patients on MTX, demonstrates the effect of age and provides first data on the effect of MTX-hold around COVID-19 vaccinations.

Using neutralising capacity and the manufacturer's cut-off, we found a slightly higher rate of vaccination responders among patients taking MTX (85.9%) than previously reported (47%–72%).[4 5] Using ROC analysis and an untreated control group, we determined an adapted cut-off value and found adequate immune response in only 40.6% of patients on MTX. Hence,

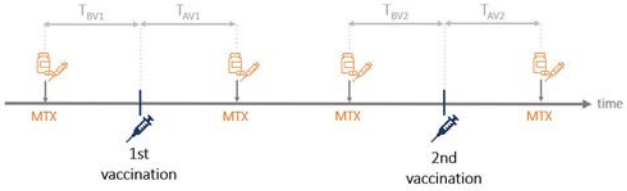

Figure 4 Visualisation of analysed time intervals. Time between methotrexate (MTX) intakes and COVID-19 vaccinations were assessed for each vaccination and added together to receive the total time before vaccinations ($T_{BV}=T_{BV1}+T_{BV2}$) and after vaccinations ($T_{AV}=T_{AV1}+T_{AV2}$). The MTX interval was defined as the total durations between two MTX intakes at the time of vaccination ($T_{AV}+T_{BV}$).

Table 4 Association of neutralising capacity and anti-RBD-IgG concentration with MTX intake timing using linear regression analysis (n=64)*

	All patients†				Patients <60 years‡				Patients ≥60 years‡			
	β	P value	95% CI	β_{st}	β	P value	95% CI	β_{st}	β	P value	95% CI	β_{st}
Neutralisation capacity												
T_{BV}	0.00	0.976	−0.20 to 0.19	0.00	−0.05	0.749	−0.37 to 0.27	−0.06	0.04	0.807	−0.26 to 0.33	0.03
T_{AV}	**0.19**	**0.005**	**0.06 to 0.32**	**0.30**	0.09	0.301	−0.09 to 0.28	0.20	**0.24**	**0.012**	**0.06 to 0.43**	**0.32**
T_{BV} ≥10 days	−0.85	0.367	−2.73 to 1.02	−0.08	−0.36	0.789	−3.12 to 2.40	−0.05	−1.98	0.094	−4.31 to 0.35	−0.13
T_{AV} ≥10 days	**2.00**	**0.008**	**0.53 to 3.47**	**0.27**	−0.22	0.833	−2.34 to 1.91	−0.04	**2.91**	**0.001**	**1.29 to 4.53**	**0.36**
T_{BV}+T_{AV}	**0.13**	**0.035**	**0.01 to 0.25**	**0.25**	0.04	0.626	−0.13 to 0.22	0.11	**0.18**	**0.039**	**0.01 to 0.35**	**0.29**
Anti-RBD-IgG												
T_{BV}	0.80	0.244	−0.56 to 2.15	0.09	0.47	0.575	−1.24 to 2.17	0.10	1.26	0.236	−0.86 to 3.39	0.12
T_{AV}	**1.02**	**0.016**	**0.19 to 1.84**	**0.19**	0.11	0.739	−0.56 to 0.78	0.04	**1.63**	**0.036**	**0.12 to 3.14**	**0.22**
T_{BV} ≥10 days	−1.86	0.777	−14.96 to 11.24	−0.02	0.49	0.950	−15.49 to 16.47	0.01	−6.43	0.323	−19.43 to 6.57	−0.05
T_{AV} ≥10 days	**13.70**	**0.004**	**4.60 to 22.79**	**0.21**	−2.53	0.583	−11.96 to 6.90	−0.07	**20.03**	**0.005**	**6.57 to 33.50**	**0.26**
T_{BV}+T_{AV}	**0.95**	**0.003**	**0.33 to 1.58**	**0.22**	0.21	0.487	−0.41 to 0.84	0.09	**1.51**	**0.019**	**0.26 to 2.77**	**0.26**

Significant results are in bold.
*One patient who did not hold MTX could not recall on which exact day MTX was taken and was therefore only considered for calculations of T_{BV}+T_{AV} (=7 days).
†Adjusted for female, age, MTX monotherapy, MTX+prednisolone, MTX combination±prednisolone, vaccine interval.
‡Adjusted for female, MTX monotherapy, MTX+prednisolone, MTX combination±prednisolone, vaccine interval. β (unstandardised beta-coefficient); β_{st} (standardised beta-coefficient); T_{BV} (time before vaccination), time between last MTX intake and vaccination; T_{AV} (time after vaccination), time between vaccination and re-intake of MTX; T_{BV}+T_{AV}, MTX interval at the time of vaccination.
MTX, methotrexate.

we confirmed the observations from previous studies that the antibody response is reduced under MTX therapy.[4 5] In contrast, others described no effect of MTX on vaccination response.[6 7] These varying results may be due to a lower effect size of MTX on vaccination response compared with other immunosuppressive therapies such as rituximab or mycophenolate, different test systems and statistical analyses used and other influencing factors such as age and pausing of MTX therapy.

We determined young age, MTX-hold and longer vaccine interval as the main factors improving antibody response after vaccination. The negative influence of age on vaccination response was already known.[20 21] However, the consideration of age was not yet differentiated in previous studies investigating immune response under MTX therapy. Therefore, our data allow the assumption that continuous MTX intake and old age are potentiating negative factors. The positive effect of a longer vaccine interval on humoral immune response is in line with previously published works.[22 23] These results were statistically significant in t-test for both antibody testing systems, but in the generalised linear model only for anti-RBD-IgG levels. This discrepancy is likely due to the higher statistical power of the t-test.

Patients who held MTX for at least one vaccination had a significantly higher immune response than those who continued MTX, which has not yet been described for COVID-19 vaccination. Nevertheless, our findings are in line with studies by Park *et al* investigating the effect of MTX-hold on the immune response to influenza vaccination.[11] More detailed analysis showed that time after vaccination is crucial, which was also described by Park *et al* who recommended an MTX discontinuation of 2 weeks after influenza vaccination.[12 13] In our study, we found a minimum time of 10 days after vaccination to be critical for immune response in patients ≥60 years. Additionally, the positive effect of MTX-hold was only statistically significant for patients 60 years or older. An effect also in younger patients might be observed in a larger cohort.

A strength of our study was that we validated all our neutralisation test results with an additional test system measuring anti-RBD-IgG levels. The latter defined four more patients as non-responders compared with the neutralisation test. This small number of conflicting test results is to be expected when using different test systems. The uneven distribution of gender among patients who had conflicting test results caused our analyses to suggest a significant influence of gender on the neutralisation result. This may be due to a statistical artefact and the effect of gender should be interpreted with caution.

This study has limitations. Since data regarding the MTX intake schedule during vaccination were assessed retrospectively, recall bias cannot be excluded. Due to our small sample size, we had to limit factors in the multivariable logistic regression modelling, which may lead to bias and residual confounding. For instance, confounding due to duration from vaccination to blood sampling, disease activity or AIRD diagnosis cannot with certainty be excluded in our analyses. We did not assess disease activity and safety of pausing MTX in our cohort, but current data do not indicate a significantly higher flare occurrence or disease activity in association with MTX discontinuation of 2 weeks.[24] Also, T-cell response was not part of our study design. However, according to current studies, it can be assumed that measuring humoral vaccination response is an adequate mean to determine vaccine immunogenicity[25] and that higher antibody levels correlate with a better clinical outcome.[26 27] To address these limitations, a randomised controlled clinical trial to generate evidence for optimal management of MTX in COVID-19 vaccinations should be performed.

In conclusion, we present real-world data of clinical relevance regarding ongoing booster vaccinations. We determined age and MTX-hold as the main factors influencing antibody response during SARS-CoV-2 vaccinations and both aspects should be considered when discussing MTX regimens. Our data suggest that, if possible, patients older than 60 years of age should hold MTX for at least 10 days after receiving a COVID-19 vaccination.

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Contributors All authors contributed to the acquisition, analysis or interpretation of data and critical revision of the manuscript for important intellectual content. RB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. RB is responsible for the overall content as the guarantor. FNA, JZ, G-RB, RB were involved in the study design. Sample collection was done by ANAdS, LF, FNA, VS, AtH, JZ. Experiments and data analysis were performed by ANAdS, LF, FNA, JK, LMJ, TS, JZ, VMC, CD, G-RB and RB. ANAdS, LF, FNA and RB were responsible for tables and figures. Data interpretation was done by all authors. Statistical analyses were done by ANAdS, LF, FNA, JK and RB. Writing of the manuscript were performed by ANAdS, LF, FNA, JK, G-RB and RB. All authors were involved in critical proof reading of the manuscript.

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Competing interests VMC is named together with Euroimmun GmbH on a patent application filed recently regarding the diagnostic of SARS-CoV-2 by antibody testing.

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 applicable.

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Data availability statement All data relevant to the study are included in the article. Data are available on reasonable request.

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CLINICAL SCIENCE

Two-week methotrexate discontinuation in patients with rheumatoid arthritis vaccinated with inactivated SARS-CoV-2 vaccine: a randomised clinical trial

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ABSTRACT

Objective To evaluate the effect on immunogenicity and safety of 2-week methotrexate (MTX) discontinuation after each dose of the Sinovac-CoronaVac vaccine versus MTX maintenance in patients with rheumatoid arthritis (RA).

Methods This was a single-centre, prospective, randomised, investigator-blinded, intervention study (NCT04754698, CoronavRheum) including adult patients with RA (stable Clinical Disease Activity Index (CDAI) ≤10, prednisone ≤7.5 mg/day) randomised (1:1) to withdraw MTX (MTX-hold) for 2 weeks after each vaccine dose or maintain MTX (MTX-maintain), evaluated at day 0 (D0), D28 and D69. Coprimary outcomes were anti-SARS-CoV-2 S1/S2 IgG seroconversion (SC) and neutralising antibody (NAb) positivity at D69. Secondary outcomes were geometric mean titres (GMT) and flare rates. For immunogenicity analyses, we excluded patients with baseline positive IgG/NAb, and for safety reasons those who flared at D28 (CDAI >10) and did not withdraw MTX twice.

Results Randomisation included 138 patients with 9 exclusions (5 COVID-19, 4 protocol violations). Safety evaluation included 60 patients in the MTX-hold and 69 patients in the MTX-maintain group. Further exclusions included 27 patients (13 (21.7%) vs 14 (20.3%), p=0.848) with positive baseline IgG/NAb and 10 patients (21.3%) in MTX-hold with CDAI >10 at D28. At D69, the MTX-hold group (n=37) had a higher rate of SC than the MTX-maintain group (n=55) (29 (78.4%) vs 30 (54.5%), p=0.019), with parallel augmentation in GMT (34.2 (25.2–46.4) vs 16.8 (11.9–23.6), p=0.006). No differences were observed for NAb positivity (23 (62.2%) vs 27 (49.1%), p=0.217). At D28 flare, the rates were comparable in both groups (CDAI, p=0.122; Disease Activity Score in 28 joints with C reactive protein, p=0.576), whereas CDAI >10 was more frequent in MTX-hold at D69 (p=0.024).

Conclusion We provided novel data that 2-week MTX withdrawal after each dose of the Sinovac-CoronaVac vaccine improves anti-SARS-CoV-2 IgG response. The increased flare rates after the second MTX withdrawal may be attributed to the short-term interval between vaccine doses. This strategy requires close surveillance and shared decision making due to the possibility of flares.

Key messages

What is already known about this subject?

⇒ Temporary methotrexate (MTX) withdrawal for 2 weeks after influenza vaccine improved immunogenicity in patients with rheumatoid arthritis (RA) without worsening disease activity.

What does this study add?

⇒ This is the first randomised study showing that 2-week MTX withdrawal after each 28-day interval Sinovac-CoronaVac vaccine dose improves anti-SARS-CoV-2 immunogenicity.

⇒ However, the strategy was associated with higher flare rates (Clinical Disease Activity Index (CDAI) >10) after the second dose of vaccine.

How might this impact on clinical practice or future developments?

⇒ These novel results reinforce the recommendation of temporary MTX withdrawal after Sinovac-CoronaVac vaccine in patients with RA with CDAI ≤10, with close disease activity surveillance.

⇒ The increased flare rates after the second MTX withdrawal may be due to the short-term interval between vaccine doses.

INTRODUCTION

The SARS-CoV-2 virus has caused worldwide health, social and economic crisis with death toll reaching millions.[1] Brazil has been one of the most impacted countries, with mortality surpassing 600 000 subjects in October 2021.[2] The WHO has recommended the emergency use of the Sinovac-CoronaVac vaccine (Sinovac Life Sciences, Beijing, China),[3] an inactivated vaccine against SARS-CoV-2 CN02 strain and also one of the first approved vaccines in Brazil, accounting for over 70 million doses as of October 2021.[4] The effectiveness of this vaccine was demonstrated in a large study with 10.2 million people in whom the protective effect for hospitalisation, intensive care unit admission and COVID-19-related death was over 85%.[5]

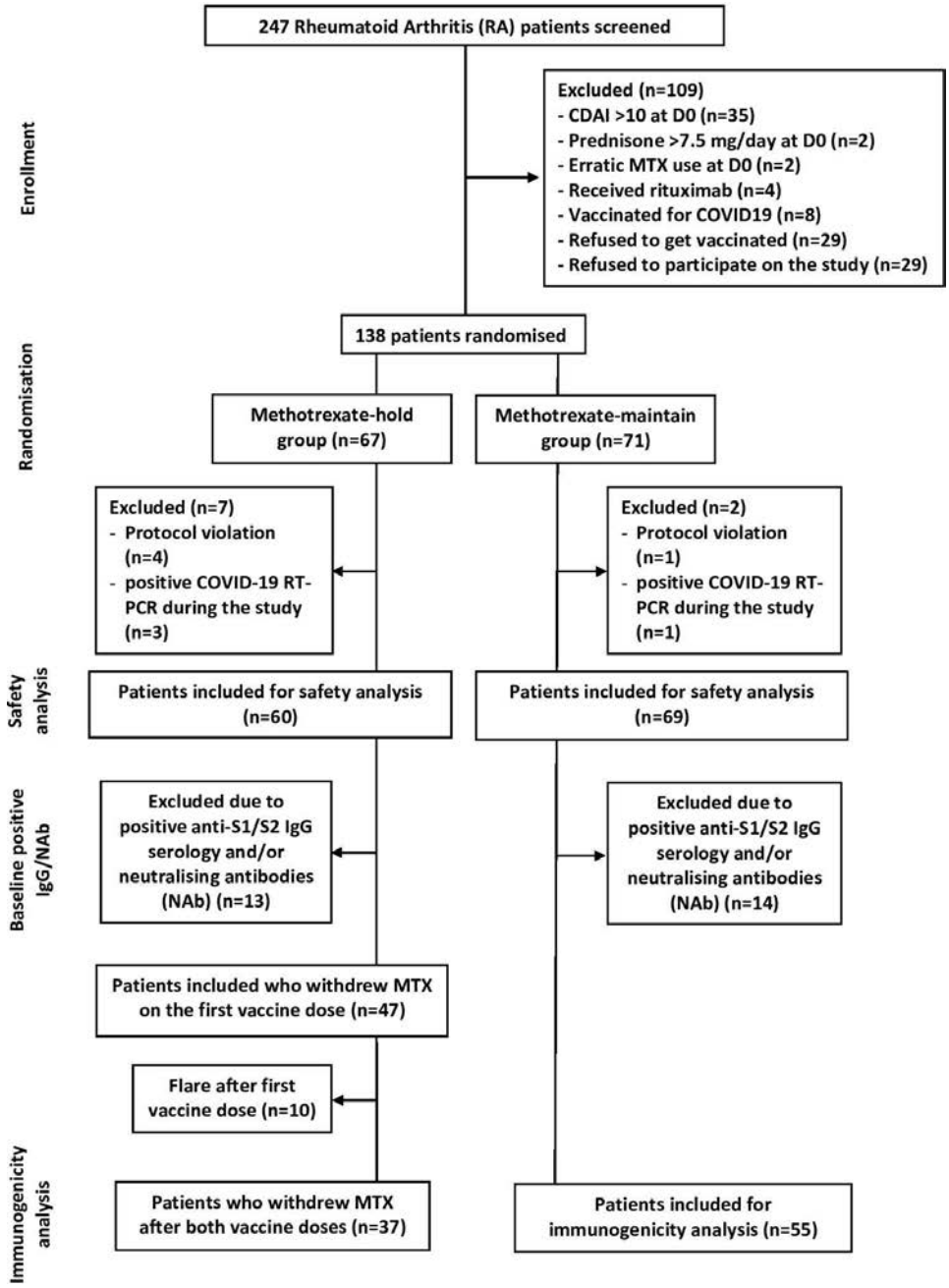

Figure 1 Modified CONSORT flow diagram. CDAI, Clinical Disease Activity Index; CONSORT, Consolidated Standards of Reporting Trials; D0, day 0; RT-PCR, reverse transcriptase PCR.

Patients with rheumatoid arthritis (RA) are at higher risk of hospitalisation and death by COVID-19 due to comorbidities[6–8] or immunosuppressive treatments.[6–9] Moreover, patients with RA have reduced immunogenicity to COVID-19 vaccines[10–21] when using rituximab,[11–17] abatacept,[11 12 17] methotrexate (MTX)[11–13 18–21] and glucocorticoids.[10–12 18]

Temporary immunosuppressant withdrawal is suggested as a possible strategy to enhance vaccine immunogenicity in patients with autoimmune rheumatic diseases (ARD).[19 20 22] In this context, Park *et al*[19 20] demonstrated that the discontinuation of MTX improved immunogenicity of the annual influenza vaccines in patients with RA, concluding that the interruption of two MTX doses after vaccination was safe and equally effective as holding four MTX doses.[23 24] Due to these results, recommendations have emerged favouring the withdrawal of MTX for 1–2 weeks after COVID-19 vaccines.[25 26] However, to this date, no comparative study has assessed the impact of this intervention on immunogenicity and disease activity after any SARS-CoV-2 vaccination schedule.

Therefore, this trial aimed to evaluate the immunogenicity and safety of a 2-week MTX discontinuation after each dose of the Sinovac-CoronaVac vaccine in patients with RA with remission/low disease activity compared with age and sex balanced RA group who maintained the drug.

METHODS

Study design

This was a single-centre, randomised, investigator-blind, intervention study performed at the rheumatology outpatient clinic of a tertiary centre. All patients with RA fulfilled the American

Table 1 Baseline characteristics of patients with rheumatoid arthritis according to MTX interruption (MTX-hold) or MTX maintenance (MTX-maintain)

	Patients for safety analyses			Patients for immunogenicity analyses		
	MTX-hold (n=60)	MTX-maintain (n=69)	P value	MTX-hold (n=37)	MTX-maintain (n=55)	P value
Current age, years	61 (52–70.5)	58 (49–68)	0.395	59 (45–68)	59 (51.5–68)	0.828
Female sex	51 (85.0)	63 (91.3)	0.265	34 (91.9)	50 (90.9)	>0.999
Caucasian race	28 (46.7)	29 (42)	0.597	19 (51.4)	25 (45.5)	0.579
Disease parameters						
Disease duration	17 (10–30.5)	17 (10–24)	0.801	19 (10–28)	17 (10–25)	0.616
RF positivity	48 (80)	53/68* (77.9)	0.776	31 (83.8)	44 (80)	0.647
Anti-CCP positivity	27/37* (73)	35/47* (74.5)	0.877	17/22* (77.3)	26/36* (72.2)	0.670
CRP, mg/dL	4.4 (1.1–9.3)	3.7 (1.6–7.0)	0.655	5.6 (1.0–9.6)	4.0 (2.5–7.5)	0.847
CDAI	7.0 (4.0–9.0)	6.0 (3.0–8.0)	0.485	6.0 (2.0–8.0)	6.0 (3.0–8.0)	0.548
SDAI	7.1 (4.1–10.1)	6.3 (3.9–9.3)	0.380	6.8 (3.1–9.4)	6 (3.8–8.3)	0.618
DAS28-CRP	2.72 (2.10–3.15)	2.33 (1.96–2.82)	0.178	2.43 (1.80–3.15)	2.34 (2.02–2.87)	0.927
CDAI ≤2.8	11 (18.3)	10 (14.5)	0.556	10 (27)	8 (14.5)	0.139
SDAI ≤3.3	12 (20)	14 (20.3)	0.967	12 (32.4)	11 (20)	0.177
DAS28-CRP ≤2.6	30 (50)	46 (66.6)	0.055	21 (56.8)	36 (65.5)	0.400
Boolean criteria	9 (15)	14 (20.3)	0.434	9 (24.3)	12 (21.8)	0.779
Current therapy						
Prednisone	33 (55)	24 (34.8)	0.021	19 (51.4)	18 (32.9)	0.074
Prednisone dose, mg/dL	5 (4.38–5)	5 (5–5)	0.495	5 (2.5–5)	5 (5–5)	0.336
MTX dose	20 (17.5–25)	20 (15–25)	0.397	20 (15–25)	20 (15–25)	0.314
MTX 10–15 mg/week	16 (26.7)	23 (33.3)	0.411	11 (29.7)	20 (36.4)	0.509
MTX 17.5–25 mg/week	44 (73.3)	46 (66.7)		26 (70.3)	35 (63.6)	
MTX monotherapy	13 (21.7)	18 (26.1)	0.558	9 (24.3)	16 (29.1)	0.614
MTX in combination	47 (78.3)	51 (73.9)		28 (75.7)	39 (70.9)	
Leflunomide	8 (13.3)	17 (24.6)	0.105	6 (16.2)	13 (23.6)	0.389
Other sDMARD	10 (16.7)	19 (27.5)	0.140	6 (16.2)	16 (29.1)	0.156
Abatacept	7 (11.7)	9 (13.0)	0.813	6 (16.2)	7 (12.7)	0.638
Other bDMARD	18 (30.0)	14 (20.3)	0.203	11 (29.7)	9 (16.4)	0.128

Results are expressed in median (IQR) and n (%).
Continuous data are compared using Mann-Whitney U test and categorical variables with χ^2 or Fisher's exact test, as appropriate, as two-sided analyses.
For safety analyses, all patients who adhered to the protocol were included. For immunogenicity analyses, patients with baseline positive S1/S2 IgG were excluded from both groups and patients with CDAI >10 at day 28 who withdrew MTX only once were excluded only from the MTX-hold group.
*Percentages calculated according to available data.
Anti-CCP, anticyclic citrullinated peptides; bDMARD, biologic disease-modifying antirheumatic drugs; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS28-CRP, disease activity score with 28 joints and C reactive protein; MTX, methotrexate; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; sDMARD, synthetic disease-modifying antirheumatic drugs.

College of Rheumatology/European League Against Rheumatism criteria for classification of RA,[27] agreed to participate in the study and signed informed consents. The protocol is part of a larger study of immunosuppressed patients with ARD (ClinicalTrials.gov: NCT04754698).[12] Patients and the public were not involved in the design, conduct, reporting or dissemination plans of the present research.

The coprimary outcomes were seroconversion (SC) rates for anti-SARS-CoV-2 S1/S2 IgG and neutralising antibody (NAb) positivity at day 69 (D69). Secondary immunogenicity outcomes were SC rates for anti-S1/S2 IgG and NAb positivity at D28, geometric mean titre (GMT) and factor increase of GMT (FI-GMT) for anti-SARS-CoV-2 S1/S2 IgG, and NAb activity at D28 and D69.

Secondary safety outcomes were longitudinal variations in disease activity scores: Clinical Disease Activity Index (CDAI),[28] Simplified Disease Activity Index (SDAI),[28] Disease Activity Score in 28 joints with C reactive protein (DAS28-CRP)[29] and frequency of adverse events related to vaccine. Exploratory outcomes were the frequency of patients with flare at D28 and D69, defined by CDAI >10[30 31] or by an increase in DAS28-CRP >1.2 (or >0.6 if the baseline DAS28 was >3.2).[32 33] Moreover, patient perception of disease activity worsening was also evaluated.

Participants

We recruited adult (≥18 years old) patients with RA diagnosis[27] with low disease activity or remission (CDAI ≤10)[28] at first vaccination day and with stable MTX dose for at least 4 weeks, both in monotherapy or in association with synthetic or biologic disease-modifying antirheumatic drugs (DMARD). The maximum allowed prevaccination oral prednisone dose was 7.5 mg/day. Patients were invited to participate after review of their electronic records in the last 3 months (recruitment up to 3 weeks before enrolment).

Exclusion criteria were acute febrile illness/symptoms of COVID-19 at vaccination, history of anaphylaxis to vaccine components, demyelinating disease, decompensated heart failure (class III/IV), blood transfusion ≤6 months, inactivated virus vaccine ≤14 days, live virus vaccine <4 weeks, denial to participate, hospitalisation, previous vaccination with any SARS-CoV-2 vaccine, reverse transcriptase PCR (RT-PCR)-confirmed COVID-19 during the study and rituximab use in the previous 12 months. Patients with prevaccination positive COVID-19 serology (anti-S1/S2 IgG and/or NAb) were excluded from immunogenicity analysis but kept for safety evaluation.

Visit schedule

Patients were evaluated in three visits: D0 (first dose of the vaccine), D28 (second dose) and D69 (6 weeks after the second

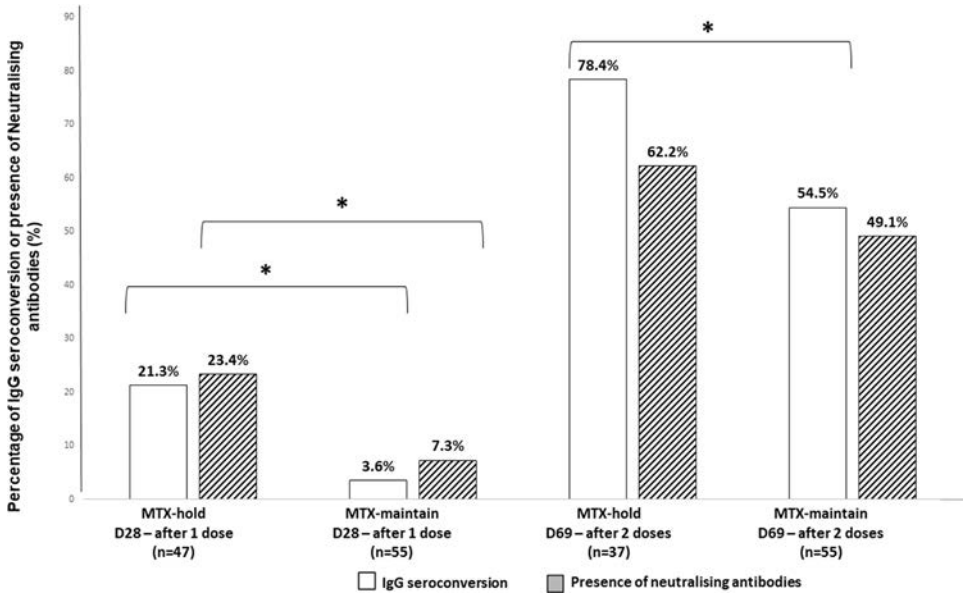

Figure 2 Frequencies of anti-SARS-CoV-2 IgG seroconversion S1/S2 and presence of neutralising antibodies at D28 and D69 in the MTX-hold and MTX-maintain groups compared using a two-sided χ^2 or Fisher's exact test, as appropriate. Data are shown as percentages. MTX-hold: baseline seronegative patients randomised to discontinue MTX after the first dose (n=47) and second dose (n=37; due to the exclusion of patients who had CDAI >10 at D28 and withdrew MTX only once). MTX-maintain: baseline seronegative patients randomised to maintain methotrexate throughout the study (n=55). *P<0.05 in comparison between groups. The number of patients in the groups is described under their designations. CDAI, Clinical Disease Activity Index; D28, day 28; D69, day 69; MTX, methotrexate.

dose). The first dose was given on 9–10 February 2021 (D0), while the second dose was on 9–10 March 2021 (D28).

The vaccination protocol included two doses of ready-to-use syringes with Sinovac-CoronaVac vaccine (batch #20200412; Sinovac Life Sciences), consisting of 3 µg in 0.5 mL of β-propiolactone inactivated SARS-CoV-2 with aluminium hydroxide adjuvant. The vaccine was administered in the deltoid muscle.

Randomisation and masking

Investigators responsible for disease activity measures, statisticians and laboratory personnel were blinded to the allocation groups. Only two researchers (CSRA and MSRS) were not blinded and were responsible for safety surveillance and patient follow-up by telephone for adherence purposes. These two investigators were not involved in disease activity measures, laboratory analysis or patient vaccination.

At D0, before the first dose of vaccine, patients were evaluated by blinded experienced rheumatologists who assessed disease activity by CDAI and rechecked the inclusion and exclusion criteria. Patients with CDAI ≤10 proceeded to the enrolment station, where the unblinded researchers revised the protocol, explained the procedures, collected the informed consent and conducted the randomisation, which was performed on the web-based software 'The REDcap Project version 10.5.0'. Allocation was generated instantaneously in a 1:1 ratio to one of the following groups: withdraw MTX for 2 weeks after each dose of the CoronaVac (MTX-hold group) or to maintain MTX continuously (MTX-maintain group).

At D28 and D69, patients were initially assessed by the unblinded researchers, checked for protocol violation and instructed not to inform their allocation groups to anyone else. Then, they proceeded for the blinded disease activity evaluation. Subsequently, they returned to the unblinded researchers and were instructed accordingly.

Intervention

At D0, the two unblinded researchers instructed patients in the MTX-hold group not to take two doses of MTX after vaccination, according to the last MTX dose. They provided a date diagram (online supplemental figure 1) informing the dates in which they would skip MTX and the date to resume its usage. At D28, patients in the MTX-hold group with CDAI ≤10 were instructed to withdraw MTX again and a new date diagram was produced. Patients with CDAI >10 in the MTX-hold group were instructed not to withdraw MTX again after the second dose of vaccine. Patients in the MTX-maintain group were instructed to continue MTX on the same day and dose throughout the study. The two unblinded researchers checked adherence to protocol by telephone contact with all patients in the weeks following both vaccine doses.

Adding or changing DMARD therapy was not allowed until D69, although patients were permitted to use analgesics, non-steroidal anti-inflammatory drugs or prednisone up to 10 mg/day in case of disease activity worsening.

Laboratory analyses

Blood samples (30 mL) were collected immediately before each vaccine dose (D0 and D28) and 6 weeks after the second dose (D69). Serum samples were stored at −70°C. IgG antibodies against the SARS-CoV-2 S1/S2 proteins were measured using a chemiluminescent immunoassay (Indirect ELISA, LIAISON, DiaSorin, Italy). SC was defined as positive serology, measured in arbitraty units per milliliter (AU/mL) (≥15.0 AU/mL).[34 35] GMT and 95% CI were calculated attributing the value of 1.9 AU/mL to undetectable levels (<3.8 AU/mL). FI-GMT was calculated as the ratio of the IgG titre after vaccination to the IgG titre before vaccination. Detection of NAb was performed using the SARS-CoV-2 surrogate virus neutralisation test (sVNT) Kit (GenScript, Piscataway, New Jersey, USA).[36] NAb activity was defined as the percentage of inhibition of the interaction between the

receptor-binding domain of the viral spike glycoprotein with the ACE-2 cell surface receptor. Positivity was defined as ≥30% inhibition of this linkage.[36] The median (IQR) of the percentage of neutralising activity was only calculated for positive samples. C reactive protein (CRP) (by the nephelometric method) was also measured.

Safety outcomes

Disease activity was checked by experienced rheumatologists, blinded to allocation groups, who assessed the following parameters: number of tender joints and number of swollen joints (both in 28 joint count), patient global assessment of disease activity (by Visual Analogue Scale), and evaluator global assessment of disease activity (by Visual Analogue Scale). With these data, CDAI was calculated. With CRP from sera collected on the same day, SDAI and DAS28-CRP were also calculated.

Patients were instructed to fill a structured diary of local and systemic symptoms after each vaccination to explore potential vaccine side effects. Adverse effect severity was classified according to the WHO definition.[37] Patients who had suggestive symptoms of COVID-19 infection had nasopharyngeal RT-PCR tests done.

Statistical analysis

The sample size calculation was based on the 2009 non-adjuvanted influenza A/H1N1 primary vaccination in a large cohort of patients with RA under MTX, which induced an SC rate of 46%.[38] Expecting an increment of 20% in the MTX-hold group,[19 20] which should achieve a 66% SC rate, with a 5% alpha error and 80% power (1:1 ratio), the minimum sample would be 96 patients per group.

Categorical variables were presented as number (percentage) and compared using χ^2 or Fisher's exact test, as appropriate. Continuous general data were presented as median (IQR) and compared using t-test or Mann-Whitney test, as appropriate. Data regarding IgG titres and disease activity scores at different time points were analysed using generalised estimating equations with normal marginal distribution and gamma distribution, respectively, and identity binding function assuming first-order autoregressive correlation matrix between moments in the comparison of the two groups, followed by Bonferroni's multiple comparisons. IgG titres were analysed as Napierian logarithm-transformed data. Multiple regression analyses were performed including SC or presence of NAb at D69 as the dependent variable and as independent variables those with $p<0.2$ in the univariate analyses. Statistical significance was defined as $p<0.05$. All statistical analyses were performed using Statistical Package for the Social Sciences V.20.0.

RESULTS

A total of 247 patients with RA fulfilled the profile on electronic chart review and were preselected. After exclusion criteria, 138 patients remained and were randomised, 67 in the MTX-hold group and 71 in the MTX-maintain group (figure 1). During the study, there were nine further exclusions: five RT-PCR-confirmed COVID-19 and four protocol violations. Therefore, the final group for all safety analyses and disease activity evaluation consisted of 60 patients in the MTX-hold and 69 in the MTX-maintain group. For the immunogenicity analyses, patients with positive anti-SARS-CoV-2 serology/NAb (13 (21.7%) vs 14 (20.3%), respectively, p=0.848) at D0 were excluded and the groups consisted of 47 (MTX-hold) vs 55 (MTX-maintain) patients for D0 and D28 analyses. Out of the 47 patients in the MTX-hold group, 10 (21.3%) had a flare on D28 and did not stop MTX the second time; thus, 37 patients finished the complete MTX withdrawal protocol and were regarded for D69 immunogenicity analyses.

The MTX-hold and MTX-maintain groups had similar age and female sex frequencies ($p>0.05$). Other demographic characteristics, comorbidities, disease duration, baseline disease activity, rheumatoid factor and anticyclic citrullinated peptide positivity, and current therapy did not differ between the two groups ($p>0.05$), except for the association with prednisone which was more frequent in the MTX-hold group in the safety analyses (p=0.021) (table 1).

Immunogenicity outcomes

Baseline anti-SARS-CoV-2 S1–S2 IgG GMT (2.1 (1.9–2.3) vs 2.0 (1.9–2.1), $p>0.999$) were similar among the groups. At D69, patients who withdrew MTX after both vaccine shots (MTX-hold, n=37) had higher SC (p=0.019) with a parallel augmentation in GMT (p=0.006) and a higher FI-GMT (p=0.007) in comparison with the MTX-maintain group (n=55) (table 2, figures 2 and 3). For NAb positivity, the difference was not

Table 2 Data on anti-S1/S2 IgG seroconversion rates, anti-SARS-CoV-2 S1/S2 IgG GMT, FI-GMT in titres, frequency of NAb and median percentage of neutralising activity in MTX-hold and MTX-maintain groups at baseline (D0) and after first (D28) and second (D69) dose of vaccine

	After first dose (D28)			After second dose (D69)		
	MTX-hold (n=47)	MTX-maintain (n=55)	P value	MTX-hold (n=37)	MTX-maintain (n=55)	P value
			Anti-S1/S2 IgG			
Seroconversion, n (%)	10 (21.3)	2 (3.6)	0.011	29 (78.4)	30 (54.5)	0.019
GMT	5.7 (4.3–7.5)	2.8 (2.3–3.5)	0.002	34.2 (25.2–46.4)	16.8 (11.9–23.6)	0.003
FI-GMT	2.9 (2.2–3.7)	1.4 (1.1–1.7)	<0.001	17.1 (12.6–23.1)	8.1 (5.8–11.4)	0.007
			Neutralising antibodies			
NAb positivity, n (%)	11 (23.4)	4 (7.3)	0.027	23 (62.2)	27 (49.1)	0.217
Neutralising activity	41.7 (37.0–46.0)	57.7 (51.8–65.9)	0.133	53 (42–68.8)	51.7 (37.8–62.2)	0.335

MTX-hold: baseline seronegative patients randomised to interrupt MTX after the first and second dose (n=47 at D28 and n=37 at D69 due to 10 patients who flared at D28 and did not withdraw MTX-twice). MTX-maintain: baseline seronegative patients randomised to maintain methotrexate stable throughout the study and who adhered to the protocol (n=69).
Seroconversion (SC) is defined as postvaccination titre ≥15 AU/mL by Indirect ELISA (LIAISON SARS-CoV-2 S1/S2 IgG). Positivity for NAb was defined as neutralising activity ≥30% (cPass sVNT Kit).
Frequencies of subjects with SC or positive NAb are presented as number (%) and were compared using a two-sided χ^2 test at prespecified time points (D28 and D69).
IgG antibody titres and FI-GMT are expressed as GMT with 95% CI. Data on IgG titres were analysed in logarithm-transformed data using generalised estimating equations with normal marginal distribution and gamma distribution, respectively, and identity binding function assuming first-order autoregressive correlation matrix between moments in the comparison of the two groups, followed by Bonferroni's multiple comparisons.
Percentages of neutralising activity among subjects with positive NAb are expressed as median (IQR). FI-GMT and neutralising activity were compared using a two-sided Mann-Whitney U test for comparison between the two groups, at prespecified time points (D28 and D69). All analyses were two-sided.
D28, day 28; D69, day 69; FI-GMT, factor increase of geometric mean titre; GMT, geometric mean titre; MTX, methotrexate; NAb, neutralising antibody; RA, rheumatoid arthritis.

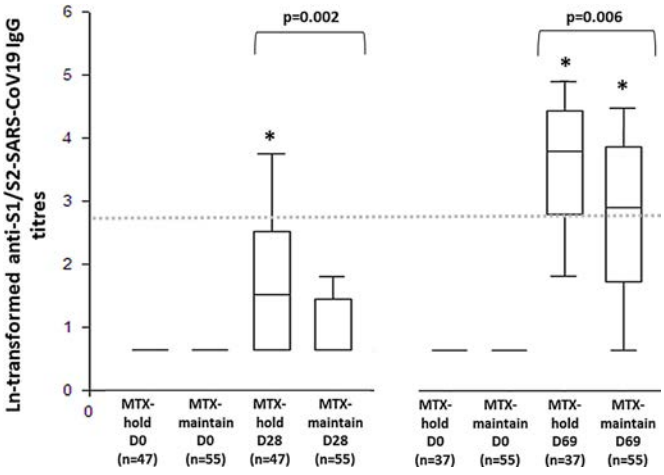

Figure 3 Box plots of anti-S1/S2 IgG titres at baseline after the first and second dose of Sinovac-CoronaVac vaccine in patients with rheumatoid arthritis according to MTX interruption (MTX-hold) or MTX maintenance (MTX-maintain). MTX-hold: baseline seronegative patients randomised to interrupt MTX after the first dose (n=47) and second dose (n=37; due to exclusion of patients who had CDAI >10 at D28 and withdrew MTX only once). MTX-maintain: baseline seronegative patients randomised to maintain methotrexate throughout the study (n=55). Analyses were performed with Napierian logarithm (ln)-transformed data using generalised estimating equations with normal marginal distribution and gamma distribution, respectively, and identity binding function assuming first-order autoregressive correlation matrix between moments in the comparison of the two groups (MTX-hold and MTX-maintain), followed by Bonferroni's multiple comparisons. The mean behaviour of the ln-transformed IgG titres was different in MTX-hold and MTX-maintain (p interaction=0.003 from D0 to D28 and p<0.001 from D0 to D69). Groups were comparable at baseline (p>0.999), but the MTX-hold group had higher mean titres at D28 (p=0.002) and D69 (p=0.006). Mean titres increased at each time point for the MTX-hold group (*p<0.001 from D0 to D28 and from D0 to D69). For the MTX-maintain group, the titres did not increase from D0 to D28 (p=0.423), but increased from D0 to D69 (*p<0.001). All analyses were two-sided. The dotted line denotes the cut-off level for positivity (ln 15 AU/mL=2.71 by Indirect ELISA, LIAISON SARS-CoV-2 S1/S2 IgG). CDAI, Clinical Disease Activity Index; D0, day 0; D28, day 28; D69, day 69; MTX, methotrexate.

significant (p=0.217), as also occurred for NAb activity (p=0.335) (table 2, figure 2).

The additional analysis at D28, after only one dose of vaccine, prior to exclusion due to flares (MTX-hold, n=47; MTX-maintain, n=55), showed that the MTX-hold group had higher SC rates (p=0.011), NAb positivity (p=0.027), GMT (p=0.002) and FI-GMT (p<0.001) (table 2, figures 2 and 3).

Assessment of factors associated with immunogenicity

In a further analysis combining both groups, the comparison of patients who had SC and those who did not seroconvert showed that older age, age ≥60 years and combination with leflunomide were negatively associated with SC, while completing the MTX withdrawal protocol (withdrawing MTX twice) was positively related to it. For NAb, only older age and age ≥60 years were negatively associated with presence of NAb (table 3). In multivariate analyses, older age (OR 0.71 (0.56–0.89) for each 5-year interval, p=0.003) and age ≥60 years (OR 0.16 (0.05–0.50), p=0.001) persisted negatively associated with SC, while MTX withdrawal twice (OR 4.6 (1.43–15.04), p=0.010) was positively associated with SC.

Disease activity

For these evaluations, the groups consisted of 60 (MTX-hold) and 69 (MTX-maintain) patients, including those with positive baseline IgG/NAb. Longitudinally, CDAI (p=0.144), SDAI (p=0.117), DAS28-CRP (p=0.718) and CRP (p=0.410) had the same behaviour in the MTX-hold and MTX-maintain groups, with worsening at D28 (p<0.001 for CDAI, SDAI and DAS28-CRP; p=0.027 for CRP), but not from D28 to D69 (p>0.999 for CDAI, SDAI and CRP; p=0.602 for DAS28-CRP) (figure 4).

At D28, no differences appeared regardless of flare definition (p>0.05) (table 4). At D69, the groups had similar rates of flares based on DAS28 variations (p=0.188). However, the MTX-hold group had more flares according to the CDAI >10 criteria (p=0.011) and more patients reported disease worsening (p=0.044). Evaluating flares at any time during the study, the same pattern was observed: no differences between the groups based on DAS28 variation (p=0.094) and a higher number of flares based on CDAI (p=0.024) and patient perception of disease worsening (p=0.022). The magnitude of variation of CDAI among patients who flared was similar between the groups (9 (4–13.5) vs 7 (4.8–10.8), p=0.456).

Vaccine side effects

Approximately half of the patients reported mild side effects, without differences between the groups. After the second dose of vaccine, myalgia (10 (16.7%) vs 3 (4.3%), p=0.037) and vertigo (7 (11.7%) vs 1 (1.5%), p=0.024) were more frequent in the MTX-hold group (online supplemental table 1).

DISCUSSION

To the best of our knowledge, this is the first randomised study to compare the impact of MTX withdrawal on the immunogenicity and disease activity of any COVID-19 vaccine in patients with RA. We demonstrated that temporary suspension is effective in increasing IgG SC and GMT levels. The observed comparable disease activity variation in the MTX-hold and MTX-maintain groups suggests that this strategy is effective in improving anti-SARS-CoV-2 IgG response, however with an increase in flare rates after the second dose of vaccine.

The study has some strengths, such as the inclusion of patients in remission/low disease activity and low prednisone doses, providing a safer condition for MTX withdrawal.[24] In addition, the randomised clinical design with allocation concealment, the blind evaluation of disease activity status and use of validated RA scores[28 29] allowed a precise analysis of flares. Moreover, the balanced distribution of demographic profile, disease features and treatment was relevant since these are known factors to influence vaccine immunogenicity and flares.[10–22] The final small sample size of the study is related to the high rate of refusals to participate and the rigorous exclusion criteria. Such small sample size underpowered the trial and is an important limitation, precluding a definite conclusion about our findings. However, the larger than expected benefit of MTX withdrawal on IgG serology allowed the identification of a significant difference between groups for SC and GMT.

We provide herein novel evidence of an increment of approximately 25% in anti-SARS-CoV-2 antibodies induced by the Sinovac-CoronaVac vaccine with temporary MTX withdrawal. Such improvement is very similar to the 20% increase first

Table 3 Baseline characteristics of patients with rheumatoid arthritis who finished the study protocol with regard to IgG antibodies and NAb after two doses of the Sinovac-CoronaVac vaccine (n=92)

	Positive IgG after two doses (n=59)	Negative IgG after two doses (n=33)	P value	Positive NAb after two doses (n=50)	Negative NAb after two doses (n=42)	P value
Demographics						
Current age, years	55 (42.5–64.5)	66 (59–69)	0.001	52.5 (40.5–67)	62.5 (55.25–69)	0.006
Age >60 years	20 (33.9)	24 (72.7)	<0.001	18 (36.0)	26 (61.9)	0.013
Female sex	53 (89.8)	31 (93.9)	0.707	47 (94.0)	37 (88.1)	0.462
Caucasian race	29 (49.2)	15 (45.5)	0.733	23 (46.0)	21 (50)	0.702
Baseline disease activity						
CDAI	5.0 (3.0–8.0)	6.0 (4.0–8.0)	0.469	6.0 (3.0–8.0)	6.0 (3.0–8.0)	0.829
SDAI	6.1 (3.1–9.1)	7.1 (4.1–9.3)	0.339	6.1 (3.2–9.4)	7.0 (3.8–9.2)	0.763
DAS28-CRP	2.43 (1.82–3.05)	2.27 (2.11–2.90)	0.843	2.45 (1.83–3.10)	2.33 (1.98–2.97)	0.742
CRP	3.3 (1.0–9.2)	8.9 (7.3–9.8)	0.154	1.6 (0.9–9.2)	7.6 (3.8–9.8)	0.161
TJC	1 (0–2)	0 (0–1)	0.086	1 (0–2)	0 (0–1)	0.259
SJC	0 (0–1)	1 (0–1)	0.297	1 (0–1)	1 (0–1)	0.727
PGA	3 (1–4)	3 (2–4)	0.491	3 (1–4)	3 (1–4)	0.570
EGA	1 (1–2)	1 (1–2)	0.223	1 (1–2)	1 (1–2)	0.766
Current therapy						
Prednisone	25 (42.4)	12 (36.4)	0.573	18 (38.0)	19 (45.2)	0.368
Prednisone dose	5 (2.5–5)	5 (5–5)	0.406	5 (2.5–5)	5 (5–5)	0.278
MTX-hold protocol	29 (49.2)	8 (24.2)	0.019	23 (46.0)	14 (33.3)	0.217
MTX monotherapy	20 (33.9)	5 (15.2)	0.053	15 (30.0)	10 (23.8)	0.506
Leflunomide	8 (13.6)	11 (33.3)	0.024	7 (14.0)	12 (28.6)	0.086
Other sDMARD	16 (27.1)	6 (18.2)	0.335	15 (30.0)	7 (16.7)	0.135
Abatacept	6 (10.2)	7 (21.2)	0.145	4 (8)	9 (21.4)	0.066
Other bDMARD	12 (20.3)	8 (24.2)	0.663	13 (26.0)	7 (16.7)	0.280

Results are expressed in median (IQR) and n (%).
Continuous data were compared using Mann-Whitney U test and categorical variables with χ^2 or Fisher's exact test, as appropriate, as two-sided analyses.
Flare was defined as CDAI >10.
bDMARD, biologic disease-modifying antirheumatic drugs (tumour necrosis factor inhibitors and tocilizumab); CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS28-CRP, Disease Activity Score with 28 joints and C reactive protein; EGA, evaluator global disease assessment; MTX, methotrexate; NAb, neutralising antibody; PGA, patient global disease assessment; SDAI, Simplified Disease Activity Index; sDMARD, synthetic disease-modifying antirheumatic drugs (sulfasalazine, hydroxychloroquine, tofacitinib); SJC, swollen joint count; TJC, total joint count.

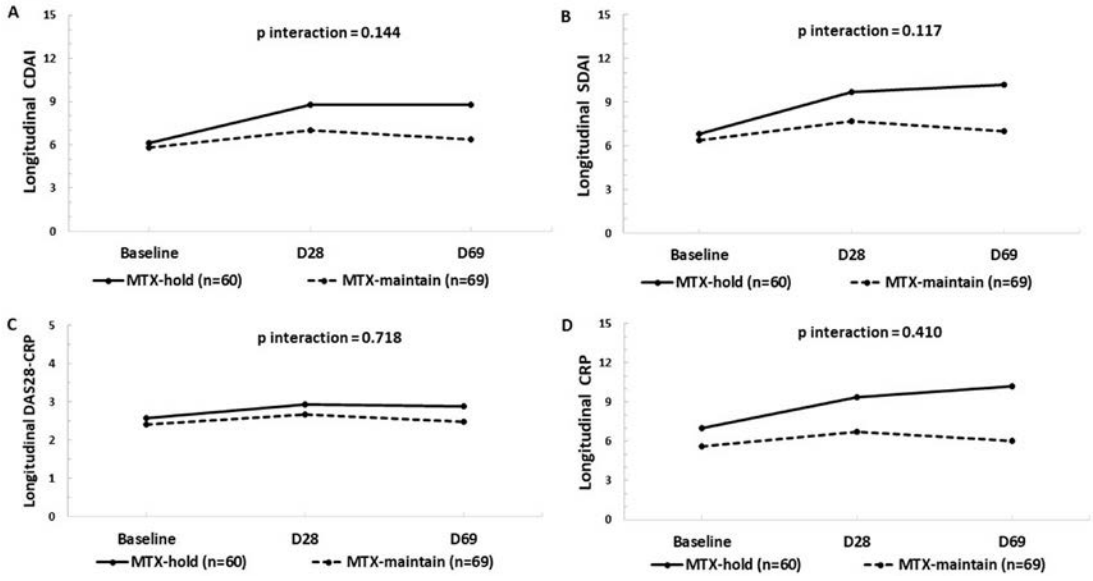

Figure 4 Analyses of continuous disease activity parameters at baseline and after the first and second dose of the Sinovac-CoronaVac vaccine in patients with rheumatoid arthritis according to MTX interruption (MTX-hold) or MTX maintenance (MTX-maintain). MTX-hold: baseline seronegative patients randomised to interrupt MTX after the first and second dose, excluding those who had CDAI >10 at D28 and withdrew MTX only once. MTX-maintain: baseline seronegative patients randomised to maintain MTX throughout the study and who adhered to the protocol. Data regarding disease activity parameters are shown as means and were analysed using generalised estimating equations with normal marginal distribution and gamma distribution, respectively, and identity binding function assuming first-order autoregressive correlation matrix between moments (D0, D28 and D69) in the comparison of the two groups (MTX-maintain and MTX-hold), followed by Bonferroni's multiple comparisons. The mean behaviour of CDAI (A), SDAI (B), DAS28-CRP (C) and CRP (D) was similar in MTX-hold and MTX-maintain throughout the study (p=0.144, p=0.117, p=0.718 and p=0.410, respectively), increasing after the first dose (p<0.001, p<0.001, p<0.001 and p=0.021, respectively) and remaining stable after the second dose (p>0.999, p>0.999, p=0.602 and p>0.999, respectively). CDAI, Clinical Disease Activity Index; CRP, C reactive protein; D28, day 28; D69, day 69; DAS28-CRP, Disease Activity Score with 28 joints; MTX, methotrexate; SDAI, Simplified Disease Activity Index.

Table 4 Disease activity analyses after the first and second dose of the Sinovac-CoronaVac vaccine in patients with rheumatoid arthritis

		After first dose (D28)	P value	After second dose (D69)	P value	At any moment	P value
ΔDAS28-CRP ≥1.2 or ΔDAS28-CRP ≥0.6 + DAS28-CRP >3.2	MTX-hold (n=60)	7 (11.7)	0.576	12 (20)	0.188	22 (36.7)	0.094
	MTX-maintain (n=69)	6 (8.7)		8 (11.6)		16 (23.2)	
CDAI >10	MTX-hold (n=60)	13 (21.7)	0.122	19 (31.7)	0.011	23 (38.3)	0.024
	MTX-maintain (n=69)	8 (11.6)		9 (13)		14 (20.3)	
Patient impression of disease flare	MTX-hold (n=60)	6 (10)	0.577	8 (13.3)	0.044	14 (23.3)	0.022
	MTX-maintain (n=69)	5 (7.2)		2 (2.3)		6 (8.7)	

For safety analyses, all patients who adhered to the protocol were included.
Results are expressed in n (%) and compared with χ^2 or Fisher's exact test, as appropriate, as two-sided analyses.
CDAI, Clinical Disease Activity Index; D28, day 28; D69, day 69; DAS28-CRP, Disease Activity Score with 28 joints and C reactive protein; MTX, methotrexate; ΔDAS28-CRP, variation of DAS28-CRP score.

described regarding MTX discontinuation for 2 weeks after influenza vaccine,[20] and could therefore partially reduce the deleterious effects in SC induced by MTX reported for the Sinovac-CoronaVac vaccine[12] and BNT162b2 mRNA COVID-19.[18 21] This immunogenicity enhancement was observed even with a high frequency of combined DMARD therapy and corticosteroids, factors that could further impair immune response to COVID-19 vaccine.[12 18] Importantly, MTX dose was comparable between the groups and all patients had doses above 10 mg/week, in line with the observation that only patients with doses greater than 7.5 mg/week benefited from MTX withdrawal after influenza vaccine.[20]

Concerning combination therapy, the distribution of drugs was alike between the groups, equalising possible additional harmful effects of different DMARDs. We also deliberately excluded patients under rituximab due to well-known effect on humoral immunogenicity and the heterogeneity of phases of treatment cycles.[11–17] In this context, multiple regression analyses revealed that neither combined DMARD nor prednisone impacted the benefit of MTX temporary discontinuation.

Safety related to vaccine and MTX withdrawal intervention was carefully assessed and included several composite measures. Longitudinally, CDAI, SDAI, DAS28-CRP and CRP had similar behaviours between the groups, increasing after the first dose and remaining stable after the second dose. In fact, the increase in disease activity measures, even in the MTX-maintain group, is in accordance with the 20% flare rate of SDAI after BNT162b2 mRNA vaccination.[11]

Considering the rate of flares, the MTX-hold and MTX-maintain groups were also comparable with regard to the DAS28-CRP criteria. The similar criteria with the Disease Activity Score in 28 joints with erythrocyte sedimentation rate (DAS28-ESR) was used in previous influenza vaccine MTX withdrawal studies[19 20] and performed better than other DAS28 flare definitions according to the Outcome Measures in Rheumatology (OMERACT) initiative.[32] In our trial, however, CDAI >10 showed to be more sensitive than DAS28-CRP, detecting significantly more flares in the MTX-hold in comparison with the MTX-maintain group at D69 and at any time. The similar longitudinal behaviour of compositive measures/CRP between groups and the rate of flares at D69 in the MTX-hold group may have been downplayed by the safety strategy of not withdrawing MTX twice in patients who flared at D28. However, the short interval between vaccine doses and the close repetition of MTX holding possibly favoured the occurrence of flares.

The Sinovac-CoronaVac vaccine was well tolerated, with no severe side effects. However, the MTX-hold group reported a higher frequency of myalgia and vertigo. The former manifestation may be associated with the vaccine or related to underlying disease activity.

In conclusion, this study provides novel data that 2-week MTX withdrawal after each vaccine dose improves anti-SARS-CoV-2 IgG response to the Sinovac-CoronaVac vaccine. The increased flare rates after second MTX withdrawal may be due to the short-term interval between vaccine doses. This strategy requires close surveillance and shared decision making due to the possibility of disease activity worsening.

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Contributors CSRA, ACM-R, CGSS, EFNY, NEA and EB conceived and designed the study. EB is responsible for the overall content as the guarantor. CSRA, ACM-R, CGSS, KRB, DSD, AYS, CAS, EFNY, TP, LdVKK, GZ, RMRP, CAS and NEA reviewed the charts and selected and invited potential patients for the study. CSRA and MSRS were the two non-blinded researchers and were responsible for randomisation, enrolment, explanation of the procedures, informed consent, safety surveillance and patient follow-up by telephone for adherence purposes. ACM-R, CGSS, KRB, DSD and AYS were the blinded investigators responsible for disease activity measures. LdVKK, TP and EB organised and supervised blood collection and vaccination protocol. SGP supervised serum processing, SARS-CoV-2-specific antibody ELISA/neutralisation assays and SARS-CoV-2 RT-PCR. ACM-R, CGSS, KRB, DSD, AYS, EFNY, SGP, CAS, TP, LdVKK, GZ, RMRP, NEA and EB participated in data collection and analysis and clinical data management. CSRA, ACM-R, CGSS, EFNY, SGP, CAS, LdVKK, NEA and EB were responsible for writing and revision of the manuscript. All authors helped edit the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was performed in accordance with the principles of the Declaration of Helsinki and approved by the national ethical committee (Comissão Nacional de Ética em Pesquisa - CONEP) and institutional ethical committee (Comissão de Ética para Análise de Projetos de Pesquisa - CAPPesq) of Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Brazil (ID CAAE: 42566621.0.0000.0068). Written informed consent was obtained from all participants. Participants gave informed consent to participate in the study before taking part.

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Data availability statement All data relevant to the study are included in the article.

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Has the gout epidemic peaked in the UK? A nationwide cohort study using data from the Clinical Practice Research Datalink, from 1997 to across the COVID-19 pandemic in 2021

The burden of gout increased globally across the 20th and 21st centuries.[1] However, a study using cross-sectional datasets demonstrated stable prevalence of hyperuricaemia and gout in the USA between 2007 and 2016.[2] Additionally, given poor persistence with urate-lowering treatment (ULT), the impact of COVID-19 pandemic on ULT prescription in a nationwide cohort merits assessment to ascertain any detrimental impact.[3] The objectives of this study were to examine temporal trends in incidence and prevalence of gout, and ULT prescription between 1997 and 2021.

Anonymised data from Clinical Practice Research Datalink (CPRD), one of the largest databases of electronic health records originating during routine clinical care, were used. The study spanned from 01 January 1997 to 31 August 2021. Gout status and ULT prescriptions were ascertained using Read and product codes (online supplemental material).

Point prevalence (95% CIs) of gout on 1 July of each year was calculated with CPRD population registered on that date as denominator. Incidence (95% CI) of gout per 1000 person-years in each calendar year was calculated using number of incident cases and total follow-up period in that year. The incidence and prevalence were directly standardised to the study population for age, sex and length of registration in CPRD[3] (online supplemental material). Proportion (95% CI) of prevalent gout cases prescribed ULT within 90 days prior to 1 July in each year, and incident gout cases prescribed ULT within 1 year of diagnosis were calculated and directly standardised to the relevant study populations. Standardised rates were used to examine temporal trend using joinpoints analysis. Crude rates for 1999 and 2021 were stratified by age and sex to compare age–sex distribution of gout before and during the COVID-19 pandemic.

Data for 373 371 patients with gout were included. The standardised prevalence (95% CI) of gout increased from 0.98% (0.97% to 0.96%) in 1997 to 2.33% (2.31% to 2.35%) in 2021, with annual average percentage change (AAPC) (95% CI) 3.9% (3.3% to 4.4%) (figure 1). The standardised incidence (95% CI) of gout increased from 1.31 (1.26 to 1.37)/1000 person-years in 1997 to 1.97 (1.94 to 2.01)/1000 person-years in 2013, and reduced to 0.98 (0.94 to 1.03)/1000 person-years in 2021. The standardised prevalence of ULT prescription increased from 25.92% in 1997 to 39.53% in 2021 (AAPC (95% CI) 1.3% (1.0% to 1.5%)), whereas the proportion of incident gout cases prescribed ULT within 1 year reduced. Fewer women than men were prescribed ULT ever, and within 1 year of diagnosis, despite older age at onset and higher comorbidity burden as reported previously.[4]

The standardised prevalence of gout remained stable across the pandemic while the standardised incidence (95% CI) reduced from 1.54 (1.50 to 1.58)/1000 person-years in 2019, to 1.07 (1.00 to 1.07) and 0.98 (0.94 to 1.03)/1000 person-years in 2020 and 2021, respectively. The age–sex distribution of prevalent gout was similar in 2019 and 2021 (online supplemental figure S1). However, gout incidence was significantly lower in 2021 than in 2019 across all ages and in both sexes (online supplemental figure S1). The prevalence (95% CI) of ULT prescription in gout improved from 36.72% (36.41% to 37.02%) in 2019 to 39.53% (39.19% to 39.91%) in 2021.

The gout epidemic appears to have peaked in the UK in 2013, with a significant reduction in incidence between 2013 and 2019, that is, before the COVID-19 pandemic potentially due to reduction in alcohol and red meat consumption.[5 6] The sharp

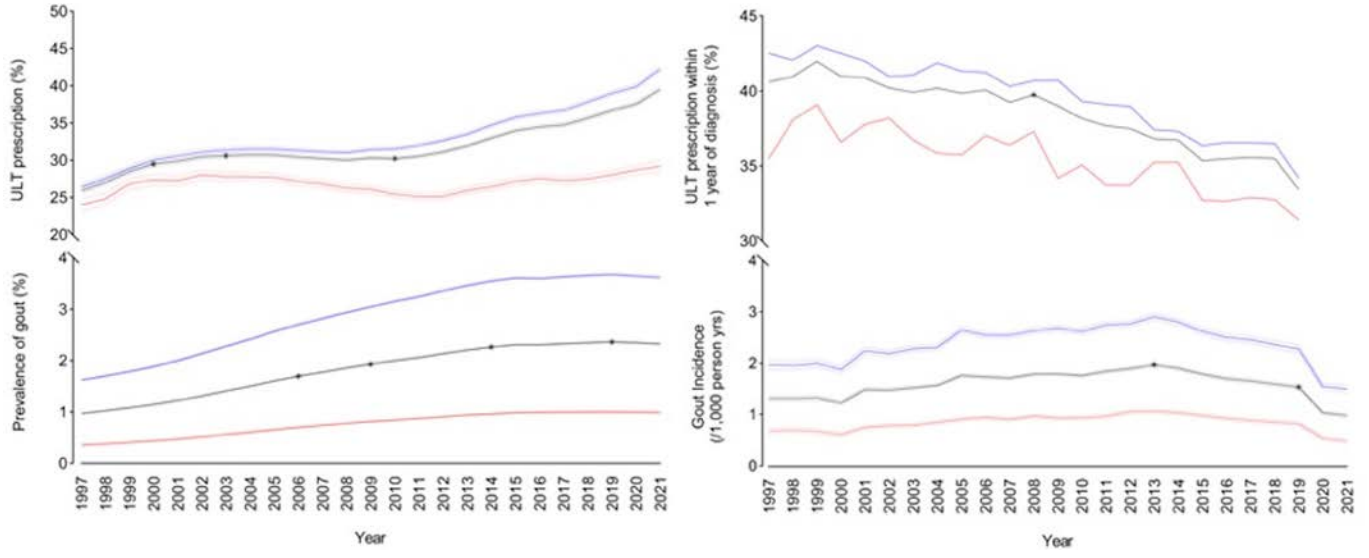

Figure 1 Temporal trend 1997–2021. Gout prevalence (lower left panel). The APCs (95% CI) were 6.6% (6.4% to 6.8%), 4.4% (2.7% to 6.0%), 3.3% (2.8% to 3.8%), 0.8% (0.2% to 1.3%), and –0.8% (–2.9% to 1.3%) in 1997–2006, 2006–2009, 2009–2014, 2014–2019, 2019–2021, respectively. Gout incidence (lower right panel). The APCs (95% CI) during 1997–2013, 2013–2019, and 2019–2021 were 2.6% (2.0% to 3.2%), –4.5% (–7.2% to –1.8%), and –23.2% (–39.0% to –3.3%), respectively. ULT prevalence (upper left panel). The APCs (95% CI) between 1997 and 2000, 2000 and 2003, 2003 and 2010, 2010 and 2021 were 4.5% (2.4% to 6.6%), 1.4% (–1.9% to 4.8%), –0.4% (–0.9% to 0.1%) and 2.3% (2.1% to 2.5%), respectively. ULT prescription within 1 year of diagnosis (upper right panel). The APCs (95% CI) between 1997 and 2008, 2008 and 2019 were –0.4% (–0.7% to –0.2%) and –1.3% (–1.5% to –1.1%), respectively. The APC (95%CI) reported are for the overall gout population. *Significant joinpoints. Blue line male, red line female, black line overall. Dotted lines 95% CI. APC, average percentage change; ULT, urate-lowering treatment.

decline in its incidence during the COVID-19 pandemic likely represents underdiagnosis, potentially because of the inability to seek healthcare due to restrictions imposed on the population and COVID-19-related workload on the health service, rather than due to improved lifestyle, as alcohol consumption increased during COVID-19 pandemic.[7] However, this may cause a surge in gout cases presenting to health services in the near future.

Overall, ULT prescriptions increased steadily since 2010, without any detrimental impact of the COVID-19 pandemic, as observed for other rheumatic diseases.[8] While encouraging, additional steps, for example, partnership with primary care and guideline implementation are needed for continued improvement. The modest increase in ULT among prevalent gout cases during the pandemic may be driven by worsening gout control, potentially due to increased alcohol consumption,[7] as prevalence of first ULT prescription within 1 year of diagnosis continued to decline in this period.

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Effectiveness and safety of combined biological therapy in patients with refractory multidomain spondyloarthritis

Combined biological therapy (CBT) is discouraged in the treatment guidelines of immune-mediated diseases due to lack of consistent evidence. The blockade of two inflammatory pathways together could increase the overall risk of infections or unexpected adverse events (AEs). Nevertheless, several reports have shown beneficial results of CBT in refractory patients with inflammatory bowel disease (IBD), with a low rate of serious AE.[1 2] Combination treatments most used include an anti-tumour necrosis factor (TNF) or anti-IL12/23 receptor (anti-IL12/23R) antibody plus an anti-α4/β7-integrin agent.

In psoriatic arthritis (PsA), previous case series have shown favourable efficacy results with CBT, mainly with an anti-TNF agent in combination with an anti-IL12/23R,[3 4] but some patients presented AE.[3 4] The experience with CBT in spondyloarthritis (SpA) is limited, usually in patients with concomitant IBD.[1 2] The aim of this work was to determine the effectiveness and safety of CBT in patients with SpA.

We present a retrospective case series, which identified nine patients with SpA under CBT, from April 2017 to October 2021, with a minimum 3-month exposure to two simultaneous biologics with different therapeutic targets (table 1). All patients fulfilled criteria for axial or peripheral SpA according to ASAS criteria and provided a written informed consent. Demographics, clinical, laboratory and safety data were collected from electronic health records. Cut-off values for a major clinical improvement were a change in Ankylosing Spondylitis Disease Activity Score-C Reactive Protein (ASDAS-CRP) >2 units and in DAS-28-CRP >1.2, whereas remission was defined as ASDAS-CRP <1.3 or DAS-28-CRP <2.6 for axial or peripheral disease, respectively.

Prior to CBT start, all patients showed high disease activity with several domain involvement and a mean disease duration

Table 1 Main clinical features and outcomes of patients receiving combined biological therapy (CBT)

Patient	Diagnosis / duration of disease	Disease phenotype	Previous bDMARDs / tDMARDs	Last bDMARD used (exposure)	Baseline disease activity at start of CBT	CBT	Number of drugs in CBT previously tested	CBT exposure (months)	Disease activity at last evaluation	Major improvement / remission
Case 1 26-year-old man	JIA subtype ERA (21 years)	Peripheral, axial, uveitis	IFX, ADA, ETN, CTZ, GOL, SEC, TCZ	SEC (5 months)	ASDAS-CRP: 4.3	SEC+GOL	2	54	ASDAS-CRP 2	Major
Case 2 60-year-old woman	Psoriatic arthritis (39 years)	Peripheral, axial, psoriasis	IFX, ETN, GOL, SEC	SEC (3 months)	ASDAS-CRP: 4.6	SEC+ETN	2	8	ASDAS-CRP 2.1*	Major
Case 3 45-year-old man	JIA subtype ERA (33 years)	Peripheral, axial, uveitis	ADA, ETN, GOL, CTZ, SEC	CTZ (5 months)	ASDAS-CRP: 4.18	ETN +SEC	2	25	ASDAS-CRP 1.3	Remission
Case 4 65-year-old woman	Psoriatic arthritis (18 years)	Peripheral, psoriasis	IFX, ADA, IXE	IXE (8 months)	DAS-28- CRP: 3.9	IXE+ADA	2	6	DAS-28-CRP: 1.4	Remission
Case 5 62-year-old man	Psoriatic arthritis (17 years)	Peripheral, psoriasis	IFX, ADA, ETN, GOL, SEC, IXE, APR	SEC (3 months)	DAS-28- CRP: 4.4	SEC+ADA	2	3	DAS-28-CRP: 4.51	None
Case 6 21-year-old man	Polyarticular JIA (19 years)+Crohn disease	Peripheral	IFX, ADA, ETN, UTK, VED	VED (28 months)	DAS-28 CRP: 4.4	VED+GOL	1	7	DAS-28-CRP: 0.96	Remission
Case 7 60-year-old woman	Psoriatic arthritis (8 years)	Peripheral, axial, psoriasis	IFX, ADA, ETN, CTZ, SEC, IXE, apr, tofa	CTZ (3 months)	DAS-28 CRP: 5	GOL +SEC	1	14	DAS-28-CRP: 2.8	Major
Case 8 31-year-old man	JIA subtype ERA (23 years)+Crohn disease	Peripheral, axial	IFX, ADA, ETN, GOL	GOL (28 months)	ASDAS-CRP: 3.9	GOL +RIS	1	11	DAS-28-CRP: 0.9	Remission
Case 9 74-year-old man	Peripheral SpA (2 years)+Crohn disease	Peripheral	IFX, ADA, UTK	UTK (9 months)	DAS-28-CRP: 6.8	UTK+GOL	1	6	DAS-28-CRP: 3	Major

*At treatment discontinuation.
ADA, adalimumab; APR, apremilast; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score-C Reactive Protein; bDMARDs, biologic disease-modifying anti-rheumatic drugs; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; CTZ, certolizumab pegol; DAS-28, Disease Activity Score-28 joints count; ERA, enthesitis-related arthritis; ETN, etanercept; GOL, golimumab; IFX, infliximab; IXE, ixekizumab; JIA, juvenile idiopathic arthritis; RIS, risankizumab; SEC, secukinumab; SpA, spondyloarthritis; TCZ, tocilizumab; tDMARDs, targeted disease-modifying anti-rheumatic drugs; TOFA, tofacitinib; UTK, ustekinumab; VED, vedolizumab.

of 20.9±11.3 years. Mean number of previous biologic/targeted drugs was 4.7±1.3. Six patients received dual anti-TNF and anti-IL17A blockade. Three patients, with concomitant Crohn disease, were prescribed an anti-TNF combined with either IL12/23R, IL23R or α4/β7-integrin antagonists.

Eight patients had previously used separately, either the combined drugs (5/9) or agents directed to previously used targets (3/9). Just in case 8, an agent directed to a new target (IL23R) was added to a previous anti-TNF (additional information in online supplemental material).

Median exposure to CBT was 14.8 (IQR: 8–19.5) months. Most patients achieved major clinical improvement and 4/9 achieved remission, allowing for stepping down of initial dose in some patients (online supplemental table S1). Only one patient experienced a transient uveitis relapse.

Interestingly, no unexpected AEs were identified and just one serious infection was recorded, not clearly attributable to CBT. A *Staphylococcus aureus* bacteremia occurred in a 60-year-old woman with multiple comorbidities who was admitted for liver decompensation, and CBT was finally discontinued. At last evaluation, seven patients still maintain CBT with favourable results and one patient under 3-month follow-up has not experienced any improvement yet.

In our case series, 8/9 cases achieved major clinical improvement, irrespective of whether the combination used previously tested drugs/targets or a new target was added to the CBT. Those findings suggest that dual inhibition could be superior to individual target monotherapies, without significant safety concerns.

Preclinical studies in animal models with dual TNF/IL17 blockade propose a synergistic effect.[5] Furthermore, our data are similar to those described in IBD studies with dual use of anti-TNF drugs and anti-IL12/23R or anti-α4/β7-integrin agents,[1 2] but no data on the association between anti-TNF and anti-IL17A are published yet. A novel bispecific antibody (ABT-122) inhibiting both TNF-α and IL-17A in PsA has shown similar efficacy results than adalimumab during a phase II trial.[6]

In conclusion, our findings suggest that CBT could be a therapeutic alternative in selected patients with multidomain and refractory SpA. We provide acceptable safety data for longer exposure periods than those described in most reported cases to date.

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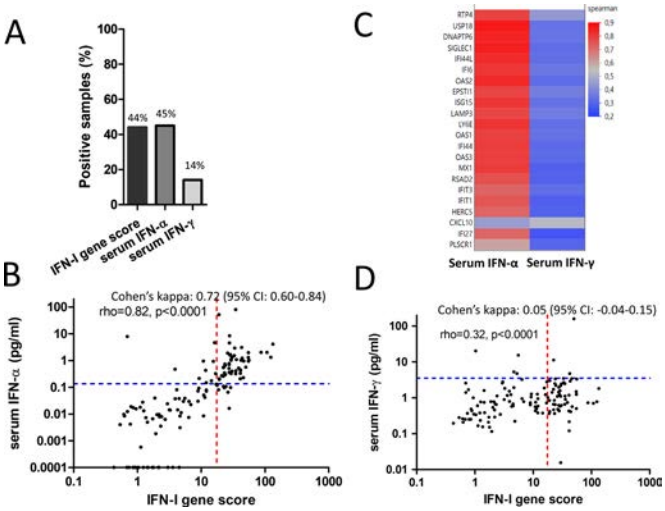

Figure 1 Prevalence, correlation and agreement between serum IFN-α and IFN-I gene score. (A) Prevalence of high serum IFN-α, serum IFN-γ and IFN-I gene score. A custom panel of 22 genes was developed and we calculated one IFN-I gene score (*IFI27, IFI44, IFI44L, RSAD2*)[2] with a cut-off≥17.5 to define high score.[3] Cut-off for high serum IFN-α was 136 fg/mL (blue line) as previously defined,[4] cut-off for high IFN-gene score was 17.5 (red line) as previously defined[3] and cut-off for high IFN-γ was 2558 fg/mL based on 3 SD above the mean from 74 HC to define elevated IFN-γ levels. (B) Spearman correlation coefficient (rho) between IFN-I gene scores and serum IFN-α values and Cohen's kappa to assess agreement between IFN-I gene score and serum IFN-α to classify patients with SLE. (C) Correlation matrix diagram of individual IFN genes with serum IFN-α and serum IFN-γ levels. Spearman correlation analysis (rho) was applied and values were condensed in a colour scale. (D) Spearman correlation (rs) between IFN-I gene score and serum IFN-γ and Cohen's kappa to assess agreement between IFN-I gene score and serum IFN-γ to classify patients with systemic lupus erythematosus (SLE). IFN, interferon.

Serum interferon-α levels and IFN type I-stimulated genes score perform equally to assess systemic lupus erythematosus disease activity

Dysregulation of type I interferon (IFN-I) signalling plays a major role in systemic lupus erythematosus (SLE) pathogenesis.[1] Selected IFN-stimulated genes (ISGs) are used to generate scores and were shown to be associated with specific clinical phenotypes, SLE activity, risk of flares and response to treatment targeting IFN-I.[2 3] IFN-I gene scores are highly heterogeneous in the number of included ISGs and are not standardised for the use in routine clinical practice. Serum IFN-α levels detected by digital ELISA by single molecule array were shown to be a promising biomarker of SLE activity[4] and predictor of flares among patients with SLE in remission.[5] IFN-γ may also play a role in SLE pathogenesis and it has been shown that several genes that are upregulated by IFN-α are upregulated also by IFN-γ.[6] In the present study, we aimed at assessing whether IFN-I gene score in blood and IFN-α or IFN-γ levels quantified by digital ELISA in serum performed similarly as biomarkers, mirroring the clinical activity of SLE. Moreover, we investigated by correlative evidence the contribution of IFN-α and IFN-γ to the expression levels of different ISGs and of an IFN-I gene score.

Gene expression was assessed by mRNA profiling using the NanoString nCounter gene expression system (NanoString Technologies, Seattle, Washington). Serum IFN-α and IFN-γ levels were quantified by digital ELISA technology (Quanterix Simoa, Lexington, Massachusetts, USA). Detailed methodology is available in online supplemental document S1. The clinical characteristics of the 133 patients with SLE included in the present study are reported in online supplemental table S1. Median age was 45.6 (range 19–78.8) years, 111 (83%) were women, 98 (74%) were Caucasians and 75 patients (56%) had an active disease using clinical Systemic Lupus Erythematosus Disease Activity Index (cSLEDAI), the contribution of low serum complement and elevated anti-dsDNA autoantibodies with a cut-off>0 to define active disease was excluded.[4]

Using the predefined cut-offs,[3 4] the prevalence of high IFN-I gene scores, elevated IFN-α and IFN-γ serum levels were 44% (58/133), 45% (60/133) and 14% (18/133), respectively (figure 1A). Serum IFN-α levels showed a highly positive correlation with the IFN-I gene scores (Spearman's correlation coefficient: rho=0.82), as well as with the expression level of

individual ISGs except for CXCL10 (figure 1B,C). In contrast, IFN-γ levels showed a weak positive correlation with IFN-I gene scores (rho=0.32) (figure 1D) and IFN-α levels (rho=0.35), as well as with the expression level of individual ISG, except for CXCL10 which showed a stronger positive correlation (rho=0.60) in accordance with a preferential induction of CXCL10 by IFN-γ (figure 1C). Using Cohen's kappa coefficient, serum IFN-α levels showed substantial agreement to classify SLE with high or low IFN-I gene scores κ=0.72 (95% CI: 0.60 to 0.84), whereas the agreement was low for IFN-γ (figure 1B,D). The sensitivity, specificity, negative and positive predictive values of serum IFN-α levels to classify SLE with high or low IFN-I gene score were 86%, 87%, 89% and 83%, respectively.

Moreover, elevated serum IFN-α levels and IFN-I gene scores were associated with active SLE, as defined by cSLEDAI>0 or SLEDAI≥4 (online supplemental figure s1–s3) and were both associated with active skin lesions, arthritis and positive anti-dsDNA Abs in multivariable analysis (online supplemental table s2). In contrast, IFN-γ was neither associated with active SLE (online supplemental figure s1) nor with active SLE characteristics (online supplemental figure s2).

Finally, IFN-I gene score AUC=0.63 (95% CI: 0.53 to 0.72) and serum IFN-α AUC=0.63 (95% CI: 0.53 to 0.72) performed similarly and significantly better than C3 levels AUC=0.42 (95% CI: 0.32 to 0.52) to discriminate inactive versus active SLE adjusted p value=0.03 and 0.03, respectively (online supplemental figure s3 and table s3).

In this study, for the first time, we show that IFN-α assessed by digital ELISA and IFN-I gene score perform equally for identifying the association of IFN-I with SLE disease activity and clinical manifestations. Remarkably, this was specific to IFN-α, since no such association was observed with serum IFN-γ levels. Of importance, we observed no association of IFN-γ serum levels with active SLE clinical features and SLEDAI. This may suggest that IFN-γ serum levels may not perform optimally as SLE biomarkers and may not support the choice of IFN-γ as therapeutic target. However, further studies are needed to explore this issue. The limitations of our study are the cross-sectional design and the relatively low number of highly active patients with SLE, which reflects real-life practice in Switzerland.

IFN-α levels measured by digital ELISA could be easier to standardise than IFN-I gene scores to characterise IFN-I overexpression in clinical practice.

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ADAMTS5 as a therapeutic target for osteoarthritis: Mendelian randomisation study

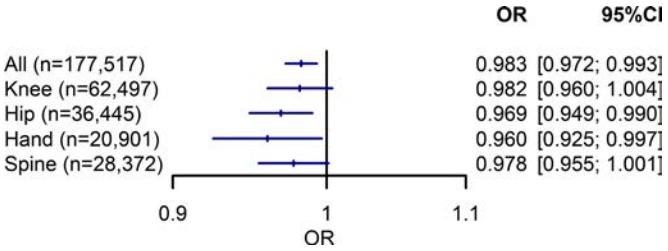

Figure 1 Mendelian randomisation estimates of the effect of genetically proxied ADAMTS5 inhibition on osteoarthritis and its subtypes.

Osteoarthritis (OA) is a progressive disease for which there is no effective disease-modifying therapy. It is characterised by articular cartilage degradation with uncontrolled proteolytic extracellular matrix destruction. The major proteoglycan in the extracellular matrix—aggrecan—is primarily cleaved by the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family of genes.[1] ADAMTS5 knockout mice have less severe cartilage destruction after induced joint instability compared with wild-type counterparts.[2] However, ADAMTS5 regulation differs in humans,[1] for whom the therapeutic role of ADAMTS5 inhibition is yet unclear. Although several ADAMTS5 inhibitors have been patented, the sole phase II trial (NCT03595618) did not demonstrate benefit for imaging or pain outcomes in knee OA.

Natural variation in the gene that encodes a protein drug target can offer insight into the clinical effects of perturbing that target pharmacologically.[3] The random allocation of genetic variants at conception means that such Mendelian randomisation (MR) analyses are robust to the confounding and reverse causation that can hinder causal inference in traditional epidemiological study designs.[4] As genetic proxies for ADAMTS5 function, we selected uncorrelated (r^2 <0.05) missense (protein coding) variants within the *ADAMTS5* gene that have been previously associated with plasma ADAMTS5 levels at genome-wide significance ($p<5\times10^{-8}$) in a study of 997 European ancestry individuals.[5] We considered the association of these missense variants with higher plasma ADAMTS5 levels to represent biological support that they adversely affect protein function to increase circulating protein levels. The genetic associations of the variants with OA were investigated in the largest genome-wide association study meta-analysis to date (177 517 cases; 649 173 controls), which also considered subtypes: knee (62 497 cases), hip (36 445), spine (28 372) and hand (20 901).[6] MR estimates for both variants were combined using the inverse variance-weighted method. Colocalisation analysis was performed to investigate possible genetic confounding through linkage disequilibrium underlying any observed MR associations. Full details are provided in online supplemental material 1.

Two missense variants (rs2830585 and rs226794, full descriptions in online supplemental material 1) were used as genetic instruments for plasma ADAMTS5 levels. Each SD increase in plasma ADAMTS5 (proxying reduced activity) was significantly associated with reduced risk of all OA types (OR 0.983, 95% CI 0.972 to 0.993; p=0.005), hip (OR 0.969; 95% CI 0.949 to 0.990; p=0.004) and hand (OR 0.960; 95% CI 0.925 to 0.997; p=0.032) OA (figure 1). For each outcome, the posterior probabilities of a shared causal variant driving plasma ADAMTS5 levels and OA were greater in magnitude than the probability of distinct causal variants (online supplemental table S2).

Results of this genetic investigation support ADAMTS5 inhibition as a therapeutic target for reducing OA risk. A key limitation of our study is that the precise effects of the two considered missense variants on ADAMTS5 function are unknown and our assumption that higher protein level reflects reduced function is unproven. However, mechanistic studies of ADAMTS5 make the alternative causal direction (reduced ADAMTS5 function being detrimental for OA) biologically unlikely. Further studies are needed to replicate these findings in other ancestries and to test for the presence of effect heterogeneity of targeting ADAMTS5 across OA subtypes.

A plethora of animal and *in vitro* human chondrocyte studies have highlighted ADAMTS5 as a promising drug target over the past two decades, yet little supportive evidence has yet emerged from human studies. Using large-scale population genetic data, this study provides evidence of a causal effect of ADAMTS5 on clinical OA phenotypes, beyond biomarker or cellular surrogates. Studies of drug development programmes have highlighted that targets with genomic support have a higher rate of success. In summary, results of this genetic analysis support ADAMTS5 as a promising disease-modifying OA drug that should be prioritised in clinical development.

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An extraordinary 75 years of EULAR

The European Alliance of Associations for Rheumatology (EULAR) has reached yet another remarkable milestone, not only in the contribution to medical advances in rheumatology, but also in the development, maintenance and adherence of a scientific alliance for the last 75 years, dedicated to improving the lives of people with rheumatic and musculoskeletal diseases (RMDs).

In today's global climate, achievements such as these are ever more significant, wherefore EULAR's President, Professor Annamaria Iagnocco, is proud to applaud this milestone and comments on EULAR's prevalence and perseverance:

> EULAR has made great strides in the last 75 years, and I am particularly proud of the outstanding achievements we have accomplished over the past years, despite the volatile global climate. From detriments to public health from the pandemic to war and tragedy in politics – the EULAR family has persevered and displayed their dedication through fostering excellence in research, education, and many more activities in rheumatology. We have stood together, in alliance, over many generations, and I could not be prouder to welcome this anniversary in Copenhagen this year, the city where we held our first Congress.

Since its foundation in 1947 in Copenhagen, EULAR has participated in a variety of advances and noteworthy medical developments in the field of rheumatology. Starting in the late 1940s, progress in the field began with the development of anti-inflammatory, immune-modulating and disease-modifying drugs. This medical leap transpired with the introduction of glucocorticoids. Moving into the 1960s, the first-ever application of methotrexate, a disease-modifying drug for persons living with rheumatoid arthritis, revolutionised the treatment and management of chronic inflammatory diseases. Even today, glucocorticoids and methotrexate are still considered pillars for treatment of inflammatory diseases. Another turning point for persons living with RMDs was the 'invention' of monoclonal antibodies in 1975. This development led to the remarkable breakthrough of specifically designed drugs (target drugs), such as the tumour necrosis factor (TNF)-alpha inhibitors, which then became available for treatment of many persons living with RMDs during the late 1990s and 2000s, and more recently of other treatments targeting molecules and cytokines involved in the inflammatory process, which ultimately leads to joint destruction and disability. Other contributions followed, such as the recognition that early diagnosis and treatment that is targeted on remission leads to substantially better outcomes, allowing for a broad range of targeted therapies. Additionally, consistent innovation in medical technology contributed to advances in imaging and specific biomarkers for the early diagnosis and follow-up of diseases, which have recently become available in the field of RMDs.

Despite several RMDs being incurable, advances in pharmacological and other therapies in rheumatology have led to an array of cutting-edge treatments available to those affected today. If properly managed, many people living with RMDs may lead a normal life, maintain their work/life balance and look forward to a typical life expectancy. In addition to the advances in medicine and strategic management of RMDs, surgical, physical and other occupational therapies have also significantly reduced the impact of RMDs on the individual and society. An example would be total joint replacement, which has become a very pertinent option for people with severe osteoarthritis of the hip or the knee. New, minimally invasive surgical strategies enrich the therapeutic spectrum and mesenchymal stem cell transplantation may in the future presage reparative therapies.

In September 1947, the first EULAR European Congress of Rheumatology was held in Copenhagen, with 200 delegates from 16 countries. This year, EULAR will return to Copenhagen to mark their extraordinary 75th anniversary and expect delegates from more than 130 countries. In alliance with scientific societies, national organisations of people with arthritis/rheumatism and health professional associations of all the European nations, EULAR has consistently displayed their devotion to rheumatology and thus has offered a chance for those affected by RMDs to lead a normal life or, in the very least, a better quality of life. EULAR underscores the importance of combating RMDs not only by medical means, but also through a wider context of care for persons living with RMDs and a thorough understanding of their social and other needs. The EULAR Congress has become the flagship of the organisation and a forum for innovation in rheumatology. EULAR President, Professor Annamaria Iagnocco, concludes:

> Copenhagen, as EULAR's place of birth, is an exceptionally significant city for us, and we look forward to going back to a country that acknowledges our organisation and supports its strategies, aiming to reduce the impact of RMDs on those afflicted and to improve their social position and quality of life. 2022 will be an extraordinary year for EULAR, marking not only our 75th anniversary but also our first-ever hybrid congress! We cordially invite you to attend our Congress and support EULAR in our mission to improve the lives of people with RMDs.

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Error in the dosage of Methotrexate in the EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis

The EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis (AAV)[1] are a pillar in the treatment of patients with these diseases worldwide. Hence, it is of the utmost importance that information, especially dosing be correct and therefore reliable. More than in some other rheumatic diseases AAV oftentimes requires treatment from a multidisciplinary team. For physicians from other specialties dosing might not be as familiar as it is for rheumatologists.

Statement 7 of the recommendations suggests a dose of Methotrexate with 20–25 mg/kg/week for remission maintenance of AAV. This recommended dose would almost certainly be toxic and lead to complications or even death. Patients die every year from wrong dosing of Methotrexate.

I suggest that in the future, before publishing recommendations for the management of rheumatic diseases an additional layer of security be implemented by separate review of every suggested dose of every medication in the publication for mistakes or typos because every mistake, howsoever small, can have far reaching consequences for our patients.

Dennis Scheicht

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Response to: 'Error in the dosage of methotrexate in the EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis' by Scheicht

The European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of ANCA-associated vasculitis were published online on 23 June 2016.[1] The recommendations were cobadged with the European Renal Association. The Article Metrics on the journal website (available from https://ard.bmj.com/content/75/9/1583.altmetrics, accessed on 4 February 2022) record 667 citations and 119 217 downloads. During production, they were circulated extensively among the authors and postproduction in the vasculitis community. Indeed, they are the only set of EULAR recommendations to have been formally voted on by 88 other clinicians besides the task force in a formal validation exercise.[2] On behalf of the authors, we thank Dr Scheicht for his kind words as well as for drawing our attention to the typographical error regarding the dose of methotrexate.[3]

In the text following statement 4 of the recommendations, we mention that methotrexate (20–25 mg/week, oral or parenteral) may be used as an alternative to cyclophosphamide in patients with less severe disease and in those with normal renal function. In the same paragraph, we mention that oral methotrexate 20–25 mg/week was non-inferior to oral cyclophosphamide at 6 months. Unfortunately, the entire steering group and the 88 other clinicians who voted on the recommendations have all overlooked that in the text following statement 7, we have made the error of saying that methotrexate (20–25 mg/kg/week) has been effectively used for maintenance therapy after induction of remission with cyclophosphamide. This is clearly an error, and the text should read 20–25 mg/week.

Dr Scheicht has recommended that an additional layer of security be implemented in the production of EULAR recommendations. The updated standardised operating procedures for EULAR-endorsed recommendations now require that the final manuscript be sent to the chair of the standing committee for approval, following which the EULAR secretariat will send the manuscript to all members of the EULAR executive committee.[4] This was indeed an unfortunate error, and we thank Dr Scheicht once again for his diligent attention. We are in the process of updating the 2016 recommendations, and we will review the dosing of all recommended medications.

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Off-label use of tofacitinib: a potential treatment option for SAPHO syndrome

Synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome is a rare and often under-reported autoimmune disease, characterised by prominent cutaneous and articular inflammation.[1] SAPHO syndrome is initially classified within spondyloarthritis, whereas recent evidence indicated that it is preferable as a primitive inflammatory osteitis. There are currently no formal evidence-based guidelines regarding the management of SAPHO syndrome, although variable degrees of efficacy of pharmacological therapies have been previously described, including non-steroidal anti-inflammatory drugs, glucocorticoids, disease-modifying antirheumatic drugs, bisphosphonates and even antibiotics.[2] Moreover, antitumour necrosis factor (TNF), interleukin (IL)-1 receptor antagonist also showed beneficial effect to the refractory SAPHO patients.[3] Nonetheless, treatment failure or paradoxical effect is still frequent in daily practice.

Tofacitinib is a potent, Janus kinase (JAK) 1/3 inhibitor, which has been approved to treat immune-mediated diseases (IMDs), including rheumatoid arthritis, psoriatic arthritis and ulcerative colitis.[4] In light of the important pathogenic role of the JAK/signal transducer and activator of transcription (STAT) pathway in IMDs, tofacitinib is being increasingly off-label used for the rheumatic diseases, especially for conditions refractory to currently standard treatment algorithms, including dermatomyositis/polymyositis, systemic sclerosis, systemic lupus erythematosus.[5] Most recently, a pilot study conducted by Li *et al* from Peking Union Medical College Hospital, in which worldwide largest cohort of SAPHO patients have been established since 2004, retrospectively, analysed the efficacy of tofacitinib 5 mg two times per day in 12 female patients with SAPHO syndrome.[6] Overall, significant multidimensional improvements were observed regarding pain, skin lesions, systemic inflammation, quality of life and remission on MRI. Of note, tofacitinib 5 mg two times per day was also beneficial for patients with an inadequate response to anti-TNF or bisphosphonates.

The understanding of SAPHO syndrome remained extremely stagnant. Recent studies revealed the potential role of cytokine dysregulation, such as TNF-α, IL-1β, IL-8, IL-17 and IL-18.[2 7–9] The effectiveness of tofacitinib would be expected to be associated with its potent and broad suppression of cytokine network via direct and indirect manner. In addition, tofacitinib has been documented to suppress osteoclast-mediated bone resorption by inhibiting the receptor activator for nuclear factor kB ligand (RANKL) pathway.[10] The efficacy of tofacitinib strongly suggested the role of JAK-STAT signalling pathway in the pathogenesis of SAPHO syndrome. Li's study indeed provides an important therapeutic option for refractory SAPHO patients who have failed with biologics therapies, but further observation is needed due to the limitations in design and sample size. Furthermore, identifying characteristics of patients and disease subtypes which may hint benefit from tofacitinib therapy deserves consideration in the setting of the complexity and heterogeneity of SAPHO syndrome.

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Response to: 'Off-label use of tofacitinib: a potential treatment option for SAPHO syndrome' by Xie *et al*

We would like to thank Xie *et al*[1] for their interest in our paper[2] and for their insights into the possible mechanism of action of tofacitinib in synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome and the trend of stratified medicine.

As Xie *et al* highlighted, tofacitinib presented clinical and radiological efficacy in patients with SAPHO syndrome who had an inadequate response to tumour necrosis factor (TNF) inhibitors or bisphophonates. Similarly, a clinical trial proved that tofacitinib was effective in patients with TNF inhibitor-resistant psoriatic arthritis (PsA).[3] By inhibiting the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, tofacitinib modulates the network of a wide range of inflammatory cytokines, including interleukin-6 (IL-6), IL-17 and TNF-α, which were potentially involved in the pathogenesis of SAPHO syndrome.[4–10] We speculated that the multipathway inhibitory effect of tofacitinib might contribute to its efficacy in refractory SAPHO syndrome.

The heterogeneity of treatment response also raises the issue of stratified treatment approach in SAPHO syndrome. Clinical and genetic markers have been identified using machine learning to enable prediction of treatment responses to anti-TNF agents in rheumatoid arthritis.[11] Furthermore, Miyagawa *et al* proved that strategic treatment based on immunological phenotypes of the individual patient yielded a significant decrease in disease activity compared with routine treatment in PsA.[12] Given the high heterogeneity of SAPHO syndrome, we believe that further efforts in precision medicine may facilitate the understanding and management of the disease.

As mentioned by Xie *et al*, our retrospective study had a limited sample size and follow-up time. It was the first step to demonstrate a new potential treatment for SAPHO syndrome. Future controlled perspective study with a larger sample size and longer follow-up duration is required to establish the efficacy and safety of tofacitinib in SAPHO syndrome.

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Comment on 'Successful remission with tofacitinib in a patient with refractory Takayasu arteritis complicated by ulcerative colitis' by Kuwabara *et al*

We read with great interest the case report by Kuwabara *et al*.[1] With this comment, we want to share the case of a 38-year-old male patient with a long history of radiographic axial spondyloarthritis (r-axSpA)—with HLA-B27 positivity, peripheral joint involvement and skin psoriasis—complicated by Takayasu arteritis (TAK), showing a favourable response to a combination therapy of Tofacitinib (TOF) and methotrexate (MTX) with the readers of the *'Annals of the Rheumatic Diseases'*.

The r-axSpA was well-controlled under tumour necrosis factor alpha inhibiton with infliximab and MTX between 2013 and 2017 (figure 1). At the beginning of 2017, he presented a worsening of his disease with peripheral arthritis/enthesitis in addition to fatigue and myalgia of the neck and shoulder region. Therefore, in 2017/2018, the treatment was changed to golimumab, and then—due to persistent symptoms—to etanercept, secukinumab and certolizumab pegol and additionally MTX was switched to sulfasalazine (SSZ). All treatment courses failed to achieve an adequate disease control (figure 1). Additionally, the patient self-administered oral prednisolone (PSL) (between 50 and 15 mg daily) during that period.

In December 2018, certolizumab pegol and SSZ were discontinued because of persistent symptoms described above, in addition to progressive weight loss as well as C reactive protein (CRP) elevation (51.3 mg/L) and treatment with TOF (5 mg two times per day) was initiated (figure 1). A week later, the patient presented with tongue swelling, muffled speech and headache. The clinical examination revealed a hypoglossal paresis. An urgent CT angiography (CT-A) showed an aneurysm of 1.7 cm of the left external carotid artery (figure 2A) and a thickening of the wall of the carotid arteries. The aneurysm was resected and TOF therapy was stopped as a precaution measure due to a temporal relationship with the acute vascular event. On the next day, the patient experienced symptoms of dysesthesia and pain in the ulnar nerve region. Ultrasound revealed an extension of the right subclavian artery, which CT-A proved to be a new pseudoaneurysm of 2.7 cm (figure 2B). This aneurysm was also resected, and a vascular prosthesis was incorporated (figure 2C).

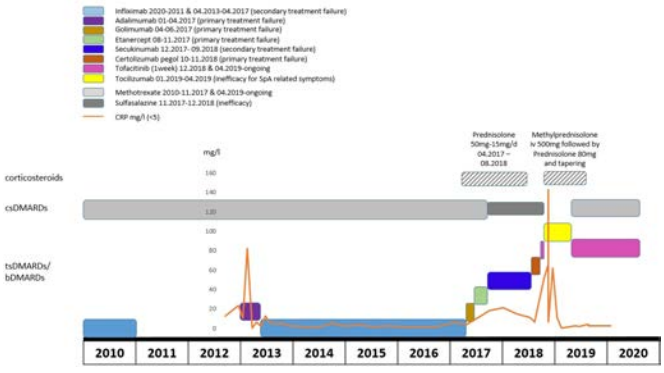

Figure 1 Treatment and CRP courses overview of the different treatment strategies and the CRP course over time. bDMARDs, biological disease modifying antirheumatic drugs; CRP, C reactive protein; csDMADRs, conventional synthetic disease modifying antirheumatic drugs; tsDMARDs, targeted synthetic disease modifying antirheumatic drugs.

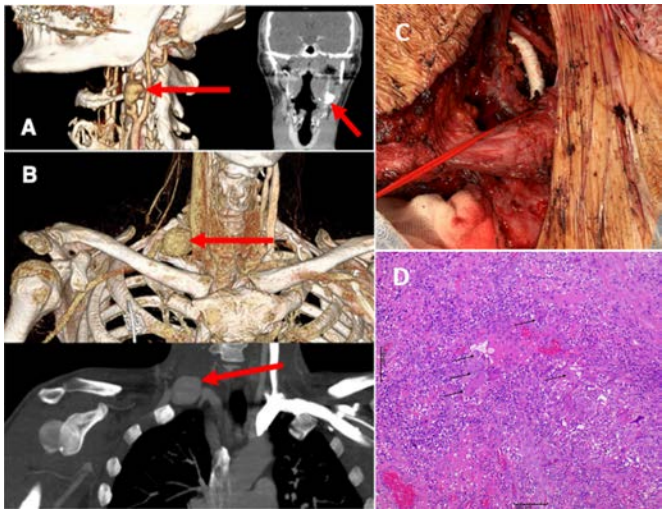

Figure 2 CTangiography, intraoperative and histological images. (A) 3D-Volume Rendering Technique (VRT) and coronal reconstructions of the neck. 1.7 cm diameter pseudoaneurysm of the left external carotid artery (red arrows). (B) 3D-VRT and coronal reconstructions of the upper thoracic aperture. 2.7 cm diameter pseudoaneurysm of the right subclavian artery (red arrows). (C) Aneurysmatectomy, replacement of the artery with subclavio-subclavian bypass using 6 mm polytetrafluorethylen (PTFE) graft. (D) Higher magnification of arterial wall reveals lymphozytes, plasma cells, macrophages and several giant cells (marked with black arrows) partially rimming necrosis.

The histopathological analysis of the aneurysm of the external carotid artery showed a lympho-histiocytic vessel wall infiltration with the presence of giant cells (figure 2D) compatible with TAK. Therefore, we started treatment with systemic corticosteroids (methylprednisolone 500 mg intravenously) and tocilizumab 8 mg/kg body weight intravenously every 4 weeks together with a tapering scheme of oral PSL starting from 80 mg daily (figure 1). However, the patient experienced a flare of his SpA-symptoms. Therefore, we switched the treatment back to TOF 5 mg two times per day together with MTX 15 mg weekly. This combination led to a rapid improvement of SpA symptoms with no new vascular episodes. The follow-up CT-A 6 months after reinitiation of the JAK-inhibition showed no further symptom progression and the CRP remained normal; PSL was tapered and subsequently stopped, while the combination therapy of TOF and MTX was continued and the patient is now in sustained clinical and laboratory remission for 12 months (figure 1).

Several cohort studies have recently reported that SpA features are common in TAK patients, and suggested potential shared genetic or immunopathogenic mechanisms.[2 3] For that reason, we believe it is utterly important to find therapeutic regimens showing efficacy for both diseases. Our case underlines the potential efficacy of JAK inhibition (in combination with MTX) in the treatment of TAK[4]; this idea is supported by the data published by Regnier *et al* in this journal presenting in vitro data as well as a case series of three TAK patients receiving baricitinib and ruxolitinib treatment,[5] and corroborates the promising data on TOF treatment in aknylosing spondylitis[6] illustrating potential future treatment options for both diseases.

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Response to: 'Comment on 'Successful remission with tofacitinib in a patient with refractory Takayasu arteritis complicated by ulcerative colitis' by Kuwabara *et al*' by Rios Rodriguez *et al*

We thank Rios Rodriguez *et al* for sharing their interesting case with us. Both of us reported that tofacitinib, a janus kinase (JAK) inhibitor, showed a favourable therapeutic effect in each patient with Takayasu arteritis (TAK) complicated by ulcerative colitis[1] or psoriatic arthritis.[2] These complications are in the same spectrum as spondyloarthritis, in which IL-23/Th17 axis plays an important pathophysiological role and the effectiveness of JAK inhibitors was demonstrated by randomised control studies.[3] As Rios Rodriguez *et al* mentioned, some population of TAK has the overlapped features with spondyloarthritis.[4] It is not unexpected if JAK inhibitors are effective in the population of TAK. But, it is unclear if JAK inhibitors are broadly useful in patients with TAK due to the heterogeneity of the disease. Th1/Th17-mediated autoimmunity is thought to be the main pathogenesis of TAK, whereas B cells and granulocytes also contribute to the development of vascular inflammation in TAK.[5] Rituximab may be more feasible for B cell-dominant TAK,[6] and tumour necrosis factor-α inhibitors may be suitable for granulocyte-dominant TAK.[7] We believe that a large-scale randomised control trial should be conducted to clarify whether JAK inhibitors are effective in the whole population of TAK. JAK inhibitors have been tested in many clinical trials as a promising drug for various rheumatic diseases.[3] If the indications for JAK inhibitors are expanded including TAK, we have to pay close attention to the safety as well as the efficacy in clinical practice. We and Rios Rodriguez *et al* described successful implementation of JAK inhibition therapy in patients with TAK.

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Bowman's capsule rupture on renal biopsy improves the outcome prediction of ANCA-associated glomerulonephritis classifications

We read the published article by Gercik *et al*[1] with great interest. In their retrospective study, they tested the existing classification systems to predict the progression to end-stage renal disease of patients with renal involvement by anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), demonstrating a better performance of the AAV renal risk score (ARRS) proposed by Brix *et al*[2] as compared with the 4-tiered glomerulocentric histological Berden's classification.[3] They suggested that the employment of baseline glomerular filtration rate in the ARRS can partly represent a possible explanation for these results. However, the evaluation of extra-glomerular histological parameters that strongly correlate with the renal outcome[4] (eg, interstitial fibrosis/tubular atrophy (IFTA)), can play a further role in the improvement of the ARRS performance. In this setting, many other classifications demonstrated the putative role of disparate histological features to predict the outcome of patients with primary (eg, IgA nephropathy[5]) and secondary (eg, lupus nephritis[6]) renal diseases, suggesting the possibility to further increase the prognostic role of the existing classification for AAV.

We retrospectively evaluated the performances of the currently used systems and investigated whether additional histological features can improve prognostic workflow of AAV. For this purpose, a retrospective, multicentric series of AAV cases have been reviewed. Each case has been independently evaluated by two renal pathologists, and classified according to the Berden's scheme and ARRS. Additional glomerular, tubulointerstitial and vascular lesions have been recorded for each case, following the previously provided definitions.[7 8] The outcome of interest was time to need for renal replacement therapy (RRT) or death, whatever occurred first. Cox proportional hazards regression models were constructed with time to composite event, loss to follow-up or censoring (30 June 2019). Time at risk started at the date of renal biopsy. The histological features, collapsed into binary variables (0 to 1=low; 2 to 3=high) and subdivided as 'active' (cellular/fibrocellular crescents, endocapillary hypercellularity, fibrinoid necrosis and Bowman's capsule rupture (BCR)) and 'chronic' (global glomerulosclerosis, fibrous crescents, segmental glomerulosclerosis, IFTA and arteriosclerosis) have been evaluated individually and in association with the currently proposed systems to assess their ability to predict the outcome. Univariate and multivariate models (HRs and 95% CIs) have been used to assess the prognostic performance of Berden's class/ARRS alone and with additional predictors (Harrell's c-statistic).

After the selection of cases with available renal biopsy, complete clinical data (at least 6 months of follow-up) and positive anti-neutrophil cytoplasmic antibody (ANCA), 52 patients have been analysed (30 (58%) males, median age 68 years (IQR 58 to 75)). ANCA showed myeloperoxidase (MPO) specificity in 31 (60%) and PR3 in 21 (31%), with a median titre of 101 U/mL (IQR 55 to 264). Six patients (12%) required dialysis at the time of the diagnosis. After the biopsy, 47 (90%) patients were treated with corticosteroids, 34 (66%) with additional immunosuppression and/or plasmapheresis (8 (15%)). During a median follow-up of 31 months (1828 person-months), 13 composite events developed (8 deaths, 5 RRT). Sixteen (31%) cases were classified as Focal, 8 (15%) as Crescentic, 24 (46%) as Mixed and 4 (8%) as Sclerotic. Patients were grouped as low (n=21, 40%), medium (n=24, 46%) and high risk (n=7, 13%) based on ARRS. Among the histological predictors tested (table 1), only BCR was significantly associated with the outcome at the univariate analysis (p=0.023). Its addition (figure 1) to the model, which included only Berden's class (c=0.67) or ARRS (c=0.62), significantly improved the prognostic performance (c=0.76 and

Table 1 Statistical analysis.

Predictor	HR (95% CI)	p-value
Univariate analysis		
Active lesions		
Endocapillary hypercellularity	1.47 (0.32 to 6.72)	0.62
Cellular/fibrocellular crescents	1.68 (0.55 to 5.15)	0.36
Glomerular fibrinoid necrosis	0.62 (0.14 to 2.78)	0.53
Bowman's capsule rupture	3.71 (1.20 to 11.44)	**0.023**
Chronic lesions		
Global glomerulosclerosis	1.49 (0.50 to 4.45)	0.47
Fibrous crescent	2.08 (0.63 to 6.84)	0.23
Segmental sclerosis	2.45 (0.79 to 7.58)	0.12
Interstitial fibrosis/tubular atrophy	1.26 (0.27 to 5.88)	0.77
Arteriosclerosis	2.79 (0.91 to 8.56)	0.07

Univariate analysis on the active/chronic lesions with reported HR and 95% CIs. Statistically significant differences are reported with a bold p-value.

Predictor	Harrell's c-statistic	HR (95% CI)	Pp-value
Multivariate analysis			
Berden's class only	0.67	3.61 (1.15 to 11.34)	**0.028**
Berden's class + BCR	0.76		
Renal risk score (Brix) only	0.62	5.25 (1.53 to 18.08)	**0.009**
Renal risk score + BCR	0.73		

Prognostic performance (with relative Harrell's c-statistic) of Berden's classes and Brix risk groups with/without the Bowman's capsule rupture (BCR) assessment and relative multivariate analysis. Statistically significant differences are reported with a bold p-value.

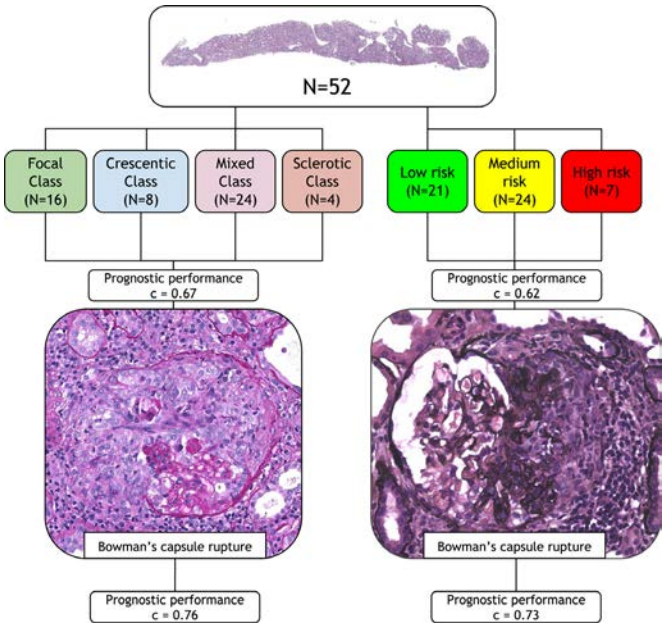

Figure 1 Panel depicting the improvement in prognostic performance of both the Berden's classification system (c=0.67) and the renal risk groups system proposed by Brix *et al* (c=0.62) after the addition of Bowman's capsule rupture as an ancillary parameter of acute renal damage (c=0.76 and c=0.73, respectively).

0.73, respectively). This has been confirmed in the multivariate model which includes Berden's class (HR 3.61, 95% CI 1.15 to 11.34; p=0.028) and ARRS (HR 5.25, 95% CI 1.53 to 18.08; p=0.009). The present study demonstrates an improved performance of prognostic systems in predicting AAV outcome after the implementation of BCR, the additional predictive role of which can partly lie in the irreversible loss of nephrons consequent to the segmental glomerulosclerosis caused by BCR.[9] Further investigations on a larger prospective cohort are required to confirm these results.

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Contributors VL ideated the study; VL and GV provided the retrospective histological assessment of renal biopsies; MF performed the statistical analysis; VL and FP drafted the paper; all the authors approved and revised the final version of the manuscript.

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Response to: 'Bowman's capsule rupture on renal biopsy improves the outcome prediction of ANCA-associated glomerulonephritis classifications' by L'Imperio *et al*

We have read delicately the report by L'Imperio *et al*.[1] We thank them for their interest in our work. Previously, we evaluated the performance of both Berden's histopathological classification and anti-neutrophil cytoplasmic antibody (ANCA) renal risk score (ARRS) in the prediction of end-stage renal disease in patients with ANCA-associated vasculitis (AAV) with baseline renal involvement and showed that ARRS might be more advantageous, possibly due to the incorporation of baseline glomerular filtration rate as a clinical parameter to the histopathological findings.[2] However, L'Imperio *et al* investigated the prognostic role of the additional glomerular, tubulointerstitial and vascular lesions to the Berden's scheme and ARRS in 52 ANCA-positive patients with AAV all had available renal biopsy, complete clinical data. In their multivariable model, the authors revealed that inclusion of Bowman's capsule rupture improved the prognostic performance of both Berden's classification and ARRS. In their analysis, the selected outcome of interest was the time to need for renal replacement therapy or death (whichever occurred first) and during a median 31 months of follow-up, 13 events developed (that eight out of them were death). However, one should keep in mind that originally both classification schemes were developed to predict the renal outcome in patients with AAV. Although baseline renal involvement is a well-known predictor of mortality in patients with AAV, cardiovascular events and infections are responsible for the vast majority of deaths[3] in those patients. Therefore, the selection of a more appropriate outcome measure might ensure more precise results.

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Pisotriquetral arthritis: 'forgotten' joint in ultrasound imaging of the wrist

We read with great interest the study of Di Matteo *et al*,[1] which highlighted the association between ultrasound (US)-detected subclinical synovitis and bone erosion with the development of inflammatory arthritis. We agree with the authors that the second and fifth metacarpophalangeal joints and the fifth metatarsophalangeal joints are the most frequent site of US-detected bone erosion.[2] However, MRI studies have reported that in rheumatoid arthritis (RA), carpal joints were affected by synovitis and erosions more frequently than metacarpophalangeal joints.[3 4] The ulnar aspect of the radiocarpal joint and the pisotriquetral joint (PTJ) are the most involved by synovitis.[5] Moreover, triquetrum is among the most frequent erosion-affected bone[3] and, according to a recent MRI investigation, seems to be the first morphological site to be affected by RA.[4]

PTJ is a small joint of the ulnar side of the wrist communicating with the radiocarpal joint in 75%–85% of the cases (figure 1A). PTJ disorders are often neglected in clinical practice,[6] and its evaluation was not taken into account by EULAR standard US assessment of the wrist.[7]

Figure 1B–D shows the sonographic findings in a patient with RA complaining of wrist pain related to PTJ synovitis and triquetral erosion. In order to achieve an optimal PTJ assessment, the operator should start with the EULAR W45 scan (ie, axial volar scan of the wrist at the level of the proximal carpal tunnel) shifting the transducer medially, over the ulnar side of the wrist. In this view, the recess of the PTJ appears small even if there is a synovitis (figure 1B). The orthogonal scan makes it possible to assess the longitudinal PTJ profile: gradually shifting the transducer allows the visualisation of the pisiform (figure 1C) and the triquetrum bone cortex (figure 1D).

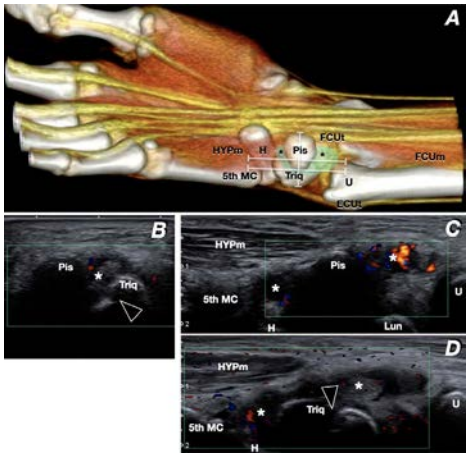

Figure 1 PTJ synovitis and Triq erosion in a patient with RA. (A) CT 3D schematic drawing of a distended PTJ (asterisks). Grey lines indicate the positions of the probe. (B) Axial directional power Doppler sonogram demonstrates synovitis of the PTJ. The recess is small, bulging between the Pis and the Triq. Note a small cortical erosion of the Triq (arrowhead). (C,D) Longitudinal directional power Doppler sonograms at the level of the Pis (C) and Triq (D) better delineate PTJ synovitis and confirm Triq erosion. Fifth MC indicates the fifth metacarpal bone. ECUt, extensor carpi ulnaris tendon; FCUm, flexor carpi ulnaris muscle; FCUt, flexor carpi ulnaris tendon; H, hamatum; HYPm, hypotenar muscle; Lun, lunatum; Pis, pisiform; PTJ, pisotriquetral joint; Triq, triquetrum; U, ulna.

Depending on anatomical variability and grade of joint distension, the articular recess may also be detected in the EULAR W36 scan (longitudinal view of the flexor carpi ulnaris).

In conclusion, we suggest that adding scanning of PTJ could improve US assessment of the wrist and may help in detecting synovitis and erosions in early inflammatory arthritis. We are aware that US has limitations in particular evaluating the more radial part of the triquetrum, for which MRI is the best choice, if clinically indicated.[6]

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Response to: 'Pisotriquetral arthritis: 'forgotten' joint in ultrasound imaging of the wrist' by Becciolini *et al*

We thank Becciolini *et al* for their interest in our recent paper,[1] in which we demonstrated that a focused ultrasound (US) examination of the classical sites for rheumatoid arthritis (RA) damage, in particular the fifth metatarsophalangeal (MTP) joints, may improve risk stratification for progression to RA in anticyclic citrullinated peptide antibody positive (CCP+) at-risk individuals.

Becciolini *et al* suggest that scanning the pisotriquetral joint (PTJ) could improve the US sensitivity for the assessment of inflammation in patients with early inflammatory arthritis (IA).[2] The logic of this suggestion is based on the results of MRI studies showing that synovitis and bone erosions can be frequently found in the carpal bones, including the PTJ, in patients with early RA.[3 4] The authors have also provided pictorial examples to show how US pathological findings (ie, synovitis and bone erosions) can be detected at this level in one patient with RA.

In recent years, US and MRI have shown the ability to predict progression to IA, and its timing, in at-risk individuals without clinical synovitis, raising important implications for the management of these individuals, including preventive approaches.[5] The US studies carried out in at-risk cohorts have used comprehensive protocols evaluating multiple pathological findings (ie, power Doppler signal, grey scale synovitis and/or bone erosions) in most or all relevant joints. Although feasible in a research setting, this can be time-consuming and therefore challenging in daily clinical practice. Which joints, and indeed how many joints, need to be evaluated for optimum predictive accuracy in at-risk individuals is still an unanswered question.

In our study, we evaluated only the joints which have been reported as the most specific for the detection of US bone erosions in RA: the second and fifth metacarpophalangeal joints and the fifth MTP joint.[6] Our study has the potential to provide to rheumatologists, who are now routinely being referred at-risk individuals in clinical practice, a valuable tool which can be readily used in the clinical setting for the management and risk stratification of these individuals. We acknowledge, however, that targeting US to only these sites of RA damage might potentially exclude other anatomical sites (ie, distal ulna or PTJ) from being evaluated which, as a result, might lead to underestimating the overall prevalence of bone erosions in CCP +at risk individuals.

Both the pisiform and triquetrum have been long known to be sites for early radiographic bone erosions in RA.[7] During an US assessment, the triquetrum would normally be scanned as part of the existing EUropean League Against Rheumatism scanning views of the ulnar-carpal aspect of the wrist with the triquetrum forming the 'carpal part'. The pisiform, however, has been a less favoured area to evaluate, unless there was a specific clinical indication to do so (eg, a site of significant pain). This practice is partly historical as US image resolution in the past was not good enough to clearly demonstrate this small region. In addition, older machines with larger transducers provided limited adequate transducer access. Anatomically, the positioning of the pisiform on the triquetrum, also precludes the comprehensive visualisation of the joint, especially in perpendicular planes, which is likely to have an impact on reliability. We also note that the PTJ, like other aspects of the wrist, is a frequent location for osteoarthritis and therefore prone to both degenerative-related bone irregularity/erosion and synovitis raising the question of lesion specificity in these areas.[8] However, we agree with Becciolini *et al*,[2] that US may visualise synovitis in the surrounding recesses of the PTJ but whether this offers any additional information to more conventional areas, needs to be further explored. In conclusion, this area warrants further investigation but more data is required before it is suggested as a standard site to evaluate.

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Comparison of MS score and HScore for the diagnosis of adult-onset Still's disease-associated macrophage activation syndrome

We read with great interest the article by Minoia *et al*,[1] which reported MAS/sJIA (MS) score, a new scoring tool for diagnosis of systemic juvenile idiopathic arthritis (sJIA)-associated macrophage activation syndrome (MAS). This new diagnostic score has raised great interest and also some concerns.[2–5] Although Wang *et al*[2] tested the MS score in a group of Chinese patients with adult-onset Still's disease (AOSD)-associated MAS, the diagnostic capacity needs to be evaluated in future.

HScore was first developed for the diagnosis of reactive haemophagocytic syndrome, which resulted from mainly haematological malignancy or infection,[6] and was ever tested in patients with MAS, which resulted from different rheumatic diseases, with good performance.[7] Since there are no studies comparing the diagnostic capability of HScore and MS score, we conducted a study to compare the capacity of HScore and MS score for the diagnosis of AOSD-associated MAS.

Patients diagnosed with AOSD during January 2012 and October 2019 in our hospital were retrospectively analysed. As there is no gold standard for diagnosing AOSD-associated MAS, the diagnosis of MAS is mainly based on the profiles of clinical and laboratory data as well as agreement of more than four rheumatologists.

We included 174 patients with pure AOSD and 35 patients with AOSD-associated MAS. Clinical and laboratory data of these two groups of patients are detailed in table 1. Patients with AOSD-associated MAS were younger than those with pure AOSD (32±11.4 years vs 36.9±13.5 years, p=0.028). More deaths were observed among patients with AOSD-associated MAS (17.1% vs 3.4%, p=0.001). Regarding clinical manifestations, patients with AOSD-associated MAS had higher incidence of central nervous system involvement, decreased blood cells, haemorrhagic manifestations, hepatomegaly and enlarged lymph nodes (p<0.05), but comparable incidence of arthritis, eruption and abnormal liver function, compared with patients with pure AOSD. As for laboratory tests, patients with AOSD-associated MAS had a relatively lower level of white blood cell count, neutrophil count, lymphocyte count, platelet count, haemoglobin, fibrinogen and erythrocyte sedimentation rate (p<0.05) and a relatively higher level of ferritin, triglycerides and liver enzyme (p<0.05).

Patients with AOSD-associated MAS had higher HScore and MS score than those with pure AOSD (table 1) . ROC curve analysis (figure 1) revealed that the HScore had a stronger ability to diagnose AOSD-associated MAS compared with MScore (AUC=0.973 and 0.865 for HScore and MS score, respectively; p<0.001). HScore of ≥120 performed best (sensitivity 90.6% and specificity 89.6%), while MS score of ≥−0.25 performed best and yielded a sensitivity of 75% and a specificity of 73%.

Our results indicate that patients with AOSD-associated MAS had higher incidence of visceral involvement and more severe disease than patients with pure AOSD, and HScore seems to perform much better than MS score for the diagnosis of AOSD-associated MAS. MS score was tested by Wang *et al*[2] that it is suitable to detect MAS in patients with AOSD; however, its cut-off value should be modified from ≥−2.1 to ≥−1.08 and yielded a sensitivity of 94.1% and a specificity of 95.0%. The different performance of MS score in AOSD may result from different patients' selection. The diagnosis of MAS by Wang *et al*[2] was mainly based on the 2004 haemophagocytic lymphohistiocytosis (HLH-2004) diagnostic criteria, which is not suitable for early recognition of MAS,[8] indicating that the patients with MAS in Wang *et al*'s study might be in a relatively late stage. We believe that we included patients with MAS in a much earlier stage.

Table 1 Features of patients with AOSD with and without MAS*

	non-MAS (n=174)	MAS (n=35)	P values
Demographic			
Age, mean±SD (years)	36.9±13.5	32±11.4	0.028
Gender (F/M)	138/36	28/7	0.927
Deaths, n (%)	6 (3.4)	6 (17.1)	0.001
Clinical manifestations			
Arthritis, n (%)	119 (68.4)	25 (71.4)	0.723
Eruption, n (%)	123 (70.7)	28 (80)	0.262
Abnormal liver function, n (%)	143 (82.2)	33 (94.3)	0.073
Decreased blood cells, n (%)	1 (0.6)	26 (74.3)	<0.001
Central nervous system involvement, n (%)	0 (0)	7 (20)	<0.001
Haemorrhagic manifestations, n (%)	0 (0)	6 (17.1)	<0.001
Splenomegaly, n (%)	36 (20.7)	8 (22.9)	0.774
Hepatomegaly, n (%)	3 (1.7)	4 (11.4)	0.016
Enlarged lymph nodes, n (%)	107 (61.5)	28 (80)	0.037
Known underlying immunosuppression	1 (0.6)	13 (37.1)	<0.001
Temperature (°C)			
38.4–39.4	51 (29.3)	3 (8.6)	0.011
>39.4	123 (70.7)	32 (91.4)	0.011
Bone marrow Hemophagocytosis	1 (0.6)	17 (48.6)	<0.001
Laboratory features			
White cell count (×10^9/L)	14.2 (3.6–50.4)	6.3 (0.2–37.7)	<0.001
Neutrophil count (×10^9/L)	12.1 (1.13–48.13)	5.2 (0–36.3)	<0.001
Lymphocyte count (×10^9/L)	1.28 (0.4–4.71)	0.7 (0.15–3.08)	<0.001
Haemoglobin (g/L)	109 (53–141)	85 (63–134)	<0.001
Platelet count (×10^9/L)	295 (34–564)	81 (8–368)	<0.001
Ferritin (ng/mL)	1813 (25–42 138)	2000 (459–217 988)	0.007
Aspartate aminotransferase (U/L)	40 (7–555)	157 (17–2888)	<0.001
Alanine aminotransferase (U/L)	37 (5–539)	143 (11–2407)	<0.001
Triglycerides (mmol/L)	1.2 (0.4–3.8)	2.56 (0.7–19.3)	<0.001
Fibrinogen (g/L)	4.3 (0.9–8.1)	1.49 (0.31–5.59)	<0.001
ESR (mm/hour)	69 (3–132)	27 (1–126)	<0.001
CRP (mg/L)	83.0 (0.27–498.9)	75.6 (1.5–250)	0.772
Scores			
HScore, median (range)	68 (33-156)	196 (98–333)	<0.001
MS score, median (range)	−1.17 (−1.26 to 2.52)	1.05 (−1.26 to 26.55)	<0.001

*Values are expressed as n (%) or median (range).
AOSD, adult-onset Still's disease; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; F, female; M, male; MAS, macrophage activation syndrome.

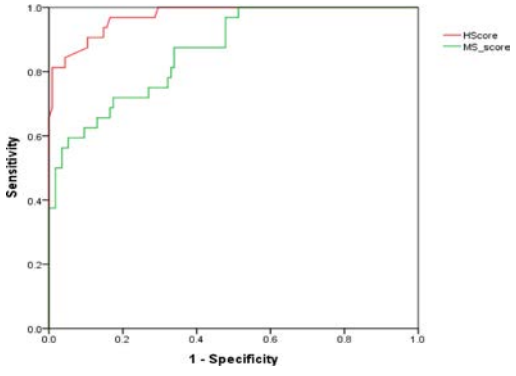

Figure 1 Roc curve of HScore and MS score. HScore=120, sensitivity=90.6%, specificity=89.6%. MS score=−0.45, sensitivity=75%, specificity=73%. AUC-HScore=0.973, AUC-MS score=0.865, p<0.001

The best cut-off value of HScore was 169, with a sensitivity of 93% and a specificity of 86% when it was developed.[6] The cut-off was set at 190.5 and yielded a sensitivity of 96.7% and a specificity of 98.4% when tested in a group of Turkish patients with MAS.[7] Our results indicate that HScore is suitable for detecting AOSD-MAS but with a lower cut-off value. Indeed, different patients' selection criteria, different disease status and different underlying diseases may result in quite different conclusions. Further studies are needed to validate these different scoring tools.

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Correction notice This article has been corrected since it published Online First. Table 1 has been amended.

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Response to: 'Comparison of MS score and HScore for the diagnosis of adult-onset Still's disease associated macrophage activation syndrome' by Zhang *et al*

We thank Zhang *et al*[1] for their interest in our MAS/sJIA (MS) score for diagnosis of macrophage activation syndrome (MAS) in systemic juvenile idiopathic arthritis (sJIA).[2] Considering that sJIA and adult-onset Still's disease (AOSD) are nowadays thought to constitute a continuum of a single disease entity[3 4] and that they share a similar risk for MAS, it is worth evaluating whether the proposed diagnostic tools are suitable to detect MAS in both illnesses.

Zhang *et al*[1] compared the diagnostic performance of the MS score with that of the HScore[5] in their retrospective series of 209 patients with AOSD, 35 of whom had MAS. The HScore is aimed at identifying a broad range of reactive haemophagocytic syndromes and has been developed in a cohort of adult patients, most of whom had infection or haematological malignancy.

By means of a receiver operating characteristic curve analysis, Zhang *et al*[1] found that the HScore had a better capacity to capture MAS than the MS score, with an area under the curve (AUC) of 0.973 and 0.865, respectively ($p<0.001$). A cut-off value ≥120 in the HScore yielded a sensitivity of 90.6% and a specificity of 89.6%, whereas the best results for the MS score (sensitivity of 75% and specificity of 73%) were obtained with a cut-off value ≥−0.25.

Although the authors' conclusion that the HScore performs better than the MS score in diagnosing AOSD-associated MAS is justified by the results of the analyses, their findings contrast with those reported by Wang *et al*,[6] who found that an MS cut-off score of ≥−1.08 led to achieving a sensitivity of 94.1% and a specificity of 95% and an AUC of 0.98 in their patients with AOSD.

This discordance may depend on differences in the characteristics of patient populations. As compared with the cohort of Zhang *et al*[1], patients with MAS included in the study of Wang *et al*[6] had a lower frequency of active arthritis (31.6% vs 71.4%), central nervous system dysfunction (1.7% vs 20%) and haemorrhagic manifestations (1.7% vs 17.1%), and a higher frequency of splenomegaly (83.3% vs 22.9%). There are also remarkable diversities between the AOSD patients with MAS in the series of Zhang *et al*[1] and the patients with sJIA-associated MAS enrolled in our study that led to the development of the MS score.[2 7] Our patients had a higher frequency of hepatomegaly (70% vs 11.4%) and splenomegaly (57.9% vs 22.9%), a lower frequency of lymphadenopathy (51.4% vs 80%), and a higher median value of ferritin (5253 ng/mL vs 2000 ng/mL).[7]

Beside these disparities, there are some caveats that hamper a thorough evaluation of the results of Zhang *et al*.[1] In table 1, the figures for some items that are part of the HScore, namely known underlying immunosuppression, temperature and bone marrow haemophagocytosis, are missing. Furthermore, the cut-off value for the MS score mentioned in the legend to figure 1 (−0.45) is different from that included in the manuscript text (−0.25).

In conclusion, the report of Zhang *et al*[1] highlights the urgent need to harmonise the diagnostic tools used to diagnose MAS in AOSD and sJIA. In order to obtain reliable and widely applicable results, this objective should be pursued by conducting multinational and multicentre prospective studies based on a uniform and standardised investigational protocol.

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Understanding bone fragility: theoretical explanation to non-physician health professionals

The European League Against Rheumatism recently established timely and highly important recommendation for non-physician health professionals regarding the prevention and management of bone fractures among older adults.[1] To support the health professionals' understanding of skeletal fragility, I would like to provide a theoretical explanation.[2 3]

First, non-physician health professionals are expected to play a role in the improvement of patient adherence to pharmacotherapy for osteoporosis.[1] Here, it should be paid attention that the effects of osteoporosis drugs except bisphosphonates with mineral binding capacity are lost rapidly after discontinuation,[4] which can be reasonably explained by functional adaptation of bone to mechanical loading during physical activity.[3] Second, the homeostatic system in the skeleton[2] can also explain why the small and transient effect of calcium supplementation on areal bone mineral density, measured by dual-energy X-ray absorptiometry, is lost after discontinuation.[5] Finally, although vigorous-intensity exercise would improve bone fragility,[6] the effect can be similarly lost after discontinuation, resulting from the skeletal adaptation to mechanical environment.[7] Long-term continuation of exercise should be therefore given priority over the intensity; for example, rapid bone loss following stroke[8] indicates the significance of even light-intensity physical activity.

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Response to: 'Understanding bone fragility: theoretical explanation to non-physician health professionals' by Sugiyama

We thank the author for his favourable and supportive comments[1] on our article.[2] We are pleased that our paper has highlighted the specific role that non-physician health professionals can play in the prevention and management of fragility fractures in people age 50 years or over and thank the author for adding theoretical explanations to support understanding of these roles.

We agree that the impact of some treatments to reduce skeletal fragility are lost after discontinuation and recognise the need for non-physician health professionals to encourage and support patients at high risk of fragility fracture in self-management and long-term behavioural change to optimise bone health, for example, adhering to antiosteoporosis medicines regimens.

Effective behavioural change interventions that support patients to engage with and continue moderate intensity physical activity (and also high intensity exercise as appropriate) for the long term, are important components of personalised treatment regimens and offer opportunities to prevent and manage fragility fractures in people 50 years or more.

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Changing the outcome measures, changing the results? The urgent need of a specific disease activity score to adult-onset Still's disease

We read with great interest the article by Kedor *et al*[1] on the efficacy of canakinumab, an interleukin (IL)−1β antagonist, on patients with adult-onset Still's disease (AOSD). In this multicentre, double-blind, randomised, placebo-controlled trial, 36 patients with active joint involvement were enrolled[1]; this is the largest clinical trial performed on AOSD so far. Moreover, the results of this trial are of considerable interest in this field, considering the challenge of arranging prospective studies on a rare disease. Despite the improvement of many articular secondary measures, the primary outcome, the proportion of patients with a clinically relevant reduction of the articular manifestation measured by change in disease activity score (ΔDAS28(ESR) >1.2) at week 12, did not achieve statistical significance.[1] Apparently, this finding seems to be in contrast with the strong scientific rationale, which is behind the study, of inhibiting IL-1β in AOSD and with the confirmed efficacy of canakinumab reported in the juvenile counterpart of AOSD.[2 3] As previously performed,[4 5] the authors used the DAS28 to assess the disease activity, selecting patients with active joint involvement. Although of importance, the assessment of articular pattern could not entirely evaluate the clinical manifestations of AOSD, characterised by both systemic and articular features. In fact, during flares, patients are frequently affected by fever, which is the expression of systemic inflammation of the disease, associated with arthritis, either oligo-arthritis or bilateral symmetrical rheumatoid arthritis-like polyarthritis, with a usual migrating pattern.[3] On these bases, it must be pointed out that this clinical issue reflects a big unmet need in the management of AOSD due to the lack of standardised outcome measures. In fact, an international agreement is still missing concerning the assessment of disease activity, the definition of refractory patients and the evaluation of remission. To overcome these limits, EULAR is supporting a specific working group devoted to develop and validate a disease activity score in AOSD, "*Development and validation of a disease activity score in adult onset Still's Disease: the DAVID project* (CLI113)". The EULAR Task Force includes experts, selected according to their field of interest and knowledge on AOSD, from a variety of European countries who are working, by a synergistic effort, to develop recommendations/points to consider for a clinical tool measuring disease activity in AOSD and a definition of remission readily transferable into clinical practice.

Presently, the mechanism of action of some new drugs supports a strong rationale for using such therapies on AOSD.[6] However, the possibility to plan clinical trials is strongly limited by the lack of specifically validated outcome measures with the consequent usage of surrogate measures, derived from other diseases, which could possibly lead to false-negative results. Furthermore, a validated score measuring disease activity would also allow effective comparisons between studies, reducing the heterogeneity of the results. Such a score might also reduce healthcare costs due to decreasing a potentially unjustified use of expensive therapeutic strategies. Finally, this specifically designed disease activity score would allow to re-assess the data of previous clinical trials to fully evaluate the efficacy of study drugs on AOSD.

In conclusion, the clinical trial by Kedor *et al*[1] is a further example of how the absence of validated measures could impair the expected positive results, despite the strong scientific rationale. Thus, the lack of standardised outcome measures is an urgent need to improve the management of patients with AOSD. In fact, the validated disease activity score, which will be generated by the EULAR Task Force, will allow researchers, on the one hand, to better and comprehensively investigate disease activity in these patients and, on the other, a potentially new repurposing of drugs which apparently did not show their entire usefulness in AOSD.

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Response to: 'Changing the outcome measures, changing the results? The urgent need of a specific Disease Activity Score to adult-onset Still's disease' by Ruscitti *et al*

We would like to thank Ruscitti *et al*[1] for their interest in our recent publication, in which we presented the results of the Canakinumab for treatment of adult onset Still's disease to achieve reduction ofarthritic manifestation (CONSIDER) trial. In this study, we investigated the efficacy of canakinumab for the treatment of patients with adult-onset Still's disease (AOSD) with articular involvement (tender and swollen joint counts≥4 each) by means of a multicentre, double-blind, randomised, placebo-controlled trial.[2] Patients were randomised to receive either canakinumab 4 mg/kg body weight (maximum 300 mg) every 4 weeks or placebo. According to the study goal, the primary endpoint was defined as the proportion of patients with a clinically relevant reduction in Disease Activity Score (DAS 28 >1.2) at week 12.

Since no controlled studies existed in this indication at that time of the study initiation, we were not able to base our statistical considerations on known facts of response rates to placebo or any immunosuppressive regimen. After careful consideration, our sample size calculation indicated that it requires a total of n=68 randomised patients to show a significant difference between the groups. Of note, due to a conditional approval of the drug for AOSD by the European Medicines Agency (EMA), which was partially based on the results of the biomarker analyses of our CONSIDER trial[3] and ethical considerations of a placebo-controlled trial in a potentially severe disease, we had to stop the trial prematurely. Thus, we did not reach the planed sample size, but recruited only 51% of the required patients. Of course, this situation had a strong impact on our statistical analysis. Unfortunately, our predictions of response rates were almost correct and it was not possible to show a significant difference between the groups with this limited number of patients. In the intention-to treat analysis, 67% in the canakinumab but also 41% in the placebo group reached the primary endpoint (p=0.18). We cannot extrapolate these results to a fully recruited study, but it is clear that the p value would be different for the same response rates with a higher patient number. The high placebo rate seems to be strange with this targeted approach in AOSD based on broad clinical experience and Ruscitti *et al* mention that this finding seems to be in contrast with the strong scientific rationale, which is behind the study, of inhibiting IL-1β in AOSD. However, we would like to point out that the placebo response rate should not be underestimated in this condition. The same problem led evidently also to a failure in the recently published study with tocilizumab in AOSD.[4]

We fully agree with Ruscitti *et al* that it is of upmost relevance to develop a new and reliable DAS for AOSD. In our study, DAS28 has been chosen as a primary outcome measure after discussion and in accordance with the health authorities (EMA) as an established score in rheumatology, which could support approval of the drug also in AOSD, especially in arthritic manifestations. At least this goal was achieved which is of great relevance to our patients. Of course, keeping in mind that AOSD is a systemic autoinflammatory disease, predominant articular manifestation characterises only a subgroup of patients. We still believe that to capture the outcome of articular manifestation, a placebo-controlled study design and even joint based scores like DAS28 or American College of Rheumatology (ACR) could be appropriate as done in the CONSIDER study. For patient with predominant systemic manifestations also other approaches should be discussed such as a flare design and a different primary outcome need to be used. One candidate would be the known Pouchot score (first published in 1991, modified by Rau in 2010), and validated in 2016, after approval of CONSIDER study protocol.[5–7] In fact, this score has been increasingly used in trials with AOSD recently. However, it is clear that also the modified Pouchot score has its limits, for example, due to the fact that the different captured domains are not weighted. In our mind, another example of an imperfect efficacy outcome was used in the tadekining alpha study.[8] Therefore, we fully agree with Ruscitti *et al* that there is still an urgent need to further improve management of patients with AOSD and a standardised outcome measure is the sine qua non condition to better characterise and evaluate disease and treatment response. The development and validation of a new DAS in AOSD: the Developement And Validation of a European League Against Rheumatism (EULAR) disease activity score in adult onset Stiull's Disease (DAVID) project supported by EULAR and convened by Giacomelli could provide the missing instrument and facilitate clinical studies is AOSD.

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Diagnostic accuracy of novel ultrasonographic halo score for giant cell arteritis: methodological issues

We were interested to read the paper authored by Dasgupta *et al* published in *Annals of the Rheumatic Diseases*.[1] In a prospective study design, 89 patients suspected of giant cell arteritis (GCA) were included. The authors used receiver operating characteristic, sensitivity, specificity and likelihood ratio (LR) for assessing the diagnostic accuracy of halo counts and halo scores and their relationship with disease severity in detecting GCA. Final clinical diagnosis after 6 months was considered as gold standard. In conclusion, they reported that both halo count and halo score can quantify the extent of vascular inflammation in GCA, and halo score has a better detecting of GCA rather than Halo count.

Although we admire this excellent study, we would like to explain some methodological issues that can cause misinterpretation. First of all, there is a difference between test research and diagnostic research. Diagnostic accuracy is focused on a test's added contribution to estimate the diagnostic probability of disease presence or absence.[2] In this way, the authors need to apply several tests and measure the performance of the new test in comparison with others. However, in the current study, the authors tended to evaluate test accuracy since they did not consider other tests and hence cannot provide information about the diagnostic added value of the test.[3] In fact, without the diagnostic added value, there is no evidence about the beneficial diagnostic yields of the new test.[4] Another limitation relates to the interpretation of the amount of LRs. Dasgupta *et al* interpreted that a positive LR greater than 6.41 and 2.0 can effectively predict the GCA and temporal artery (TA) biopsy, respectively. It should be noted that the range of LR+ is one to infinity and the higher the LR+, the more accurate the test is. Actually, an LR+ equal to 2 or 6 is a clear evidence for inaccuracy of the tests.[5] Also, assessing the diagnostic OR for GCA (halo count: 4.1, halo score: 5.40) and temporal artery biopsy (TAB) (halo count: 12.77, halo score: 9.4) confirms the inaccuracy of both tests.

Finally, for assessing diagnostic accuracy, it is important to evaluate both the discrimination and calibration of the new test. Without assessing calibration, it is not possible to compare the probability of the observed and predicted GCA and how these probabilities agree with the observed proportions of later developing disease.[6]

We thus argue that there are some methodological limitations and approaches to overcome them for assessing diagnostic accuracy; otherwise, misinterpretation cannot be avoided.

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Response to: 'Diagnostic accuracy of novel ultrasonographic halo score for giant cell arteritis: methodological issues' by Ghajari and Sabour

We thank Ghajari and Sabour for their interest in our work and appreciation of our study.[1] We have reported that the extent of vascular inflammation on ultrasound, as quantified by the halo score, is associated with ocular ischaemia in patients with giant cell arteritis (GCA).[2] Furthermore, we investigated the diagnostic accuracy of the halo score for a clinical diagnosis of GCA, as well as a positive temporal artery biopsy.[2] Here, we discuss the points raised by the authors.

First, the authors propose that our study was focused on 'test accuracy'. We fully agree with the authors on this point, as we included the term 'diagnostic accuracy' in our title and used it throughout our manuscript. Our definition of 'diagnostic accuracy' was similar to that reported in the references provided by the authors, that is, the ability of a test to discriminate between patients with the target condition and those without.[3 4] It appears that the authors use a slightly distinct definition for 'diagnostic accuracy', that is, 'a test's *added contribution* to estimate the diagnostic probability of disease presence or absence'. This is actually the definition of 'diagnostic yield', as indicated by the reference provided by the authors.[3] Sackett and Haynes have previously described four stages of diagnostic research.[5] In essence, our study falls within the third stage of diagnostic research, that is, determining whether the test distinguishes between patients with and without the target condition among those that were suspected to have the condition. We believe that Ghajari and Sabour point to the fourth and final stage of diagnostic research, that is, determining whether patients undergoing the test are doing better than similar untested patients. As emphasised in the conclusions and key messages of our study, we believe our findings warrant further investigation and validation. We agree with the authors that the investigation of the 'diagnostic yield' should be part of future research.[3]

Second, the authors indicate that we might have 'misinterpreted' the likelihood ratios (LRs) reported in our study. The authors state that the LRs obtained in our study (eg, 6.41 and 2.00) are 'clear evidence for inaccuracy of the tests'. The authors refer to a review article, which reports that good diagnostic tests have an LR of >10 or <0.1.[4] These particular LR cut-off points appear to be derived from a seminal report by Jaeschke *et al*.[6] We certainly agree that diagnostic tests with such LRs are good, as they have a strong effect on the post-test probability of the target condition. However, tests with an LR closer to 1.0 might still have an important impact on the post-test probability, as also emphasised by Jaeschke *et al*.[6] Diagnostic tests with LRs>2.0 or <0.5 may at least slightly to moderately alter the post-test probability.[6–8] For example, a positive test with a positive LR of 6.41 can increase a putative pretest probability of 50% towards a post-test probability of 87%.[6–8] As recognised by clinical guidelines for GCA,[9 10] it is well known that imaging tests for GCA do not provide absolute evidence for the presence or absence of this condition. The same is actually true for symptoms, physical signs or laboratory tests; none of which have LRs>10.0 or <0.1 for a diagnosis of GCA.[11] Overall, we do not agree with the authors' claim that an LR between 2.0 and 10.0 should be considered as 'clear evidence for inaccuracy' of a test. We therefore believe that the term 'misinterpretation' is not correct in this context.

The third point raised by the authors suggests that we should have investigated the calibration of the halo score. As described in the reference provided by the authors, calibration is the ability of a test to correctly estimate the risk or probability of a future event.[12] Thus, calibration is important for prognostic studies rather than diagnostic studies.[12] We presume that the definition of our reference standard, that is, the final clinical diagnosis after 6 months of follow-up, might have caused the impression that we performed a prognostic study. The follow-up in the context of our study, however, was performed to verify that the diagnosis at baseline was correct. Clinicians sometimes have doubt about the clinical diagnosis early in the disease, and alternative diseases explaining the symptoms occasionally become overt during the first months after the initial diagnosis. The reference standard used in our study is therefore common practice in diagnostic research on GCA.

Although we commend Ghajari and Sabour for critically evaluating our work, we believe that the points raised by the authors are not indicative of 'methodological issues' or 'misinterpretation' in our study. As emphasised in our report, the ultrasonographic halo score awaits further validation by prospective, multicentre studies.

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Correspondence to 'Hypersensitivity reactions with allopurinol and febuxostat: a study using the Medicare claims data'

We read with great interest the article by Singh and Cleveland, which the authors reported that the observed hypersensitivity reactions (HSRs) associated with allopurinol and febuxostat were not different.[1] This conclusion differs from previous studies on HSRs associated with allopurinol and febuxostat using claimed data[2] and intramural databases.[3] The discrepancy may arise from different inclusion criteria for the diagnosis of HSRs based on International Classification of Diseases, Ninth Revision (ICD-9) coding system, methods for identifying causative drugs, methods for stratification, as well as ethnicity of the involved population.

The definition of HSR in the study by Singh and Cleveland adopted ICD-9 diagnostic codes specifying eosinophilia (288.3), HSR- associated arthropathy (713.6), anaphylactic reactions (995.0) or unspecified adverse drug effect (995.2) or allergy (995.3), plus the baseline exclusion for E930 to E949.[1] On the contrary, in our previous studies, the definition of cutaneous adverse reactions (CARs) using the Taiwanese registry database involved drug-induced dermatitis (693.0), erythema multiforme (695.1) or erythematous conditions (695.89 or 695.9).[2–4] Likewise, another study based on intramural database and meta-analysis defining severe CARs as 693, 695.1 or 695.9/695.89 also suggested that the overall incidence of febuxostat-associated HSR was lower than that of allopurinol (0.2 vs 2.7 per 1000 users; $p<0.001$), with regard to these dermatological manifestations.[3] From a clinical standpoint, as allopurinol-associated HSRs or CARs are delayed type of hypersensitivity, which normally involve the onset of maculopapular eruption, drug reactions with eosinophilia and systemic symptoms, or Stevens-Johnson syndrome/toxic epidermal necrolysis,[5 6] defining HSR with ICD-9 codes 713.6, 995.0 or 995.2, should be not appropriate. This suggests that the discrepancy between these studies could be attributed to the inclusion criteria for the diagnosis of HSRs.

Previous studies have pointed out that colchicine rarely causes HSR, as its notoriety score in the algorithm of drug causality for epidermal necrolysis (ALDEN) is zero[7]; the main reason of colchicine being reported as HSR-associated drugs would be due to the fact that it is oftenly used in conjunction with allopurinol.[8] Likewise, without further algorithms to confirm drug causality among these ICD-9 coding-based analyses,[1 2] patients with allopurinol-associated HSRs who have been shifted to febuxostat treatment would also lead to the conclusion of febuxostat being counted as the culprit drug. Apart from HSR-inducing gout or hyperuricaemia medications such as allopurinol and febuxostat,[1–3] frequently prescribed drugs like non-steroidal anti-inflammatory drugs (NSAIDs) are commonly involved in HSR as well.[9] As NSAIDs are widely used and are available over the counter, most of these epidemiological studies on HSR could not rule out concurrent use of these causative drugs. Without reflective parametrics for instance, chronology, ALDEN[7] or Narenjo score with weight of notoriety,[10] studies based on ICD-9 coding system may not identify the specific causative drug among multiple used drugs. Thus, it may be hard to distinguish the most likely causative medications when considering all the taken drugs as allergens.

Although allopurinol-associated HSR has been suggested to be dose dependent,[11 12] the underlying mechanisms of febuxostat and colchicine-associated HSRs remain unclear. While Singh and Cleveland stratified the patients with drug dose cut-offs,[1] the severity of incident HSRs were not analysed. On the contrary, the other studies either stratified for respective HSR severity but adopted different codes for HSR definition,[2] or used intramural databases without stratifying the doses of the associated drugs.[3] Specifically, the conclusion that allopurinol was associated with higher risks of CARs than febuxostat in one of these studies was based on the stratification of severity.[2] This suggests that the stratification methods may attribute to the observed discrepancies.

Furthermore, the incidence rate of HSR varies among countries. For instance, the incidence rates of HSRs in the USA were estimated to be 23.7 for allopurinol, 30.7 for febuxostat and 25.6 for colchicine, per 1000 person years[1]; whereas in Taiwan, the annual incidence rates were 4.68 per 1000 new allopurinol users for HSR, 2.02 per 1000 new allopurinol users for HSR-caused hospitalisation and 0.39 per 1000 new allopurinol users for HSR-caused mortality, as stratified by severity.[4]

Particularly, the prevalence of HLA-B*58:01 allele, an allopurinol HSR-associated gene, fluctuates among countries[13]; moreover, the association of HLA-B*58:01 with allopurinol-induced HSR varies among populations.[14] It is possible that the susceptibility to febuxostat and colchicine -associated HSRs differs among ethnicities as well.

For the above reasons, we recommend that the cooperation of bedside diagnostics and laboratory is necessary to discriminate which of the causative drugs induce each hypersensitivity event, as confirmed with algorithms involving chronology, ALDEN or Narenjo score with weight of notoriety score, to compare their incident HSRs.

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Response to: 'Correspondence to "Hypersensitivity reactions with allopurinol and febuxostat: a study using the Medicare claims data' by Ma *et al*

We appreciate the interest and comments by Dr Ma and colleagues[1] on our recent publication.[2] Not surprisingly, our study results differ from their previous study.[3] We agree with their point regarding the differences in the definition of the main study outcome and the International Classification of Diseases (ICD) codes used to define them and discussed it in our paper.[2] We examined the incidence of hypersensitivity reactions using two previously published validated algorithms by Strom *et al* and Wright *et al* compared with their ICD algorithms to define cutaneous hypersensitivity reactions;[3] we are unable to locate the accuracy statistics of their algorithms in this publication. Differences in study findings with regard to the risk of these adverse outcomes with allopurinol and febuxostat indicate that in future studies, both types of definitions (ours and theirs) need to be examined simultaneously. This would make the study results robust and allow a more definitive answer to the question: is the risk of all hypersensitivity reactions, or all cutaneous hypersensitivity reactions, or severe cutaneous hypersensitivity reactions, different for allopurinol-exposed versus febuxostat-exposed populations?

We respectfully disagree with their comment that allopurinol-associated hypersensitivity reactions would have been attributed to febuxostat in error, since patients likely started febuxostat after stopping allopurinol. We required a >30-day period between prescription fills, for the definition of a new allopurinol (or febuxostat or colchicine) prescription start to avoid the issue of misattribution. This 30-day period also accounted for any residual biological effects of medications. Misclassification is always possible; however, we likely minimised it with the use of this approach.

We agree that a lot of patients may be concurrently using non-steroidal anti-inflammatory drugs (NSAIDs), which are known to be associated with hypersensitivity reactions. This could have confounded findings from all epidemiological studies to-date including our study, since most NSAIDs are available over-the-counter in most countries and could not be accounted for in any study so far. The hypersensitivity reactions seen with colchicine in our study might indicate the concomitant use of other medications (NSAIDs) not captured in our analyses; they are equally likely to be due to concomitant use of medications used for other disorders (cardiovascular disease, infections; ACE inhibitors, antibiotics, antivirals, anticonvulsants),[4 5] subclinical undiagnosed chronic conditions (not captured in Deyo-Charlson comorbidity index), drug-drug interactions and drug-disease interactions[6] that are very common in the elderly. Importantly, we are reporting associations, not causality. Establishing causality is difficult with observational studies.

We discuss and agree that the incidence of (and susceptibility to) hypersensitivity reactions likely varies by the country setting,[2] related to differences in the HLA-B*5801 allele frequencies. Analysis of severity of hypersensitivity reactions was not a study objective. Standardised documentation using scoring systems as they note in their letter can also allow for a better understanding of these outcomes in the future. The almost universal use of electronic health records should make this possible in the future.

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Correction: *EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis*

Yates M, Watts RA, Bajema IM, *et al*. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis* 2016;75:1583–94.doi:10.1136/annrheumdis-2016-209133

Under statement 7 the correct methotrexate dosage should be (20-25 mg/week).

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