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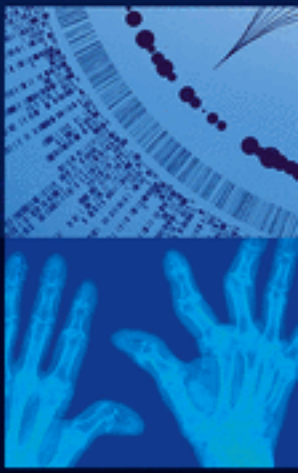

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Contact Details

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

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

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

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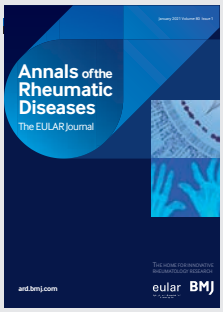

Editorial office
Annals of the Rheumatic Diseases
BMJ Publishing Group Ltd
BMA House
Tavistock Square
London WCIH 9JR,UK
T: **+44 (0)20 3655 5889**
E: **ard@bmj.com**
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MORE CONTENTS ►

Greetings from the editor 2021

Josef S Smolen

The year just past, 2020, will be remembered as the year COVID-19, elicited by SARS-CoV-2, was recognised as a pandemic, with about 120 000 reported cases and 4000 deaths globally around the ides of March.[1] Since then, a huge burden of morbidity and especially mortality has accrued, soon to exceed 65 million infected persons and 1.5 million deaths worldwide.[2] Numerous challenges have arisen, including inconsistent, frequently unpredictable and often indifferent, even frivolous approaches of politicians to the problem and varying attitudes espoused by leading experts in epidemiology and/or infectious diseases (eg, 'masks don't help' vs 'masks are very important'; or 'aim for herd immunity' vs 'herd immunity will not occur without a vaccine'; or 'lockdown is a must' vs 'no lockdown needed'). Together this has been confusing, distressing and worrisome in light of overflowing intensive care units and mass funerals in many regions of the world.

As these greetings were being written, the first vaccine, an mRNA vaccine currently named BNT162b2, has been announced effective and safe, developed by a German company, BioNtech, tested in a trial performed by a US company, Pfizer,[3] and using lipid nanoparticles for vaccine delivery provided by an Austrian company, Polymun[4]—a great success of European and transcontinental collaboration. The efficacy and safety of more vaccines have been or are soon to be revealed.

European and global collaboration was indeed also wonderful to see among rheumatologists during these first months of the COVID-19 pandemic. International databases to register patients with COVID-19 with rheumatic and musculoskeletal diseases (RMDs) were established and first analyses presented rapidly to assist clinical practice,[5] as were preliminary recommendations regarding the management of patients with RMDs during the pandemic.[6–9]

Rheumatology, Medical University of Vienna, Vienna A-1090, Austria

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

MANUSCRIPTS ON COVID-19 AND *ARD*

Just like many other journals, the *Annals of the Rheumatic Diseases* (*ARD*) was overwhelmed with submissions since March 2020, when the pandemic fully hit Europe—the number of submitted manuscripts doubled over several months compared with previous years. Just like other journals, *ARD* was confronted with the challenge to weigh the quest for the highest scientific quality, such as focusing on randomised controlled trials or requesting validation of data in independent patient cohorts, against the importance to provide our readers with rapid, first-hand information in an area where nothing was known at that time, with new information emerging weekly and sometimes daily. Indeed, publishing such information rapidly, as *ARD* and many other renowned journals did, facilitated rapid growth of knowledge, essentially in real time with every single new publication. The first *ARD* paper on COVID-19 and RMDs[10] appeared online less than 2 weeks after the announcement of the pandemic by WHO, and by the time other rheumatology journals started publishing on the topic, about a dozen reports were already fully typeset and available online for *ARD* readers.

We owe sincere thanks to the referees who were willing to expedite the review process of the many submitted extended and concise reports or letters related to COVID-19—about a handful of reviewers provided their assessments within 1–3 days; thank you, thank you! And my gratitude goes also to the publisher and BMJ staff for making extraordinary efforts to bring the papers online rapidly in a print-edited version—the time between acceptance and online publication was often just a few days; importantly, all COVID-19-related papers have been, and continue to be, made freely accessible to the public.

I am also very grateful to the Associate Editors for their support during these times and especially for the thorough assessments offered, always balanced by mature reflection on the trade-offs mentioned above, of which the referees were fully aware. Meanwhile a broad knowledge base on COVID-19 has accumulated in medicine generally and rheumatology in particular. Consequently, such studies are no longer judged primarily by how the information base can be expanded with critical open-mindedness for the delicate situation of newly emerging data at the beginning of a pandemic, but are now required to be performed, once again, with highest scientific rigour.

When one searches 'Pubmed' for publications on COVID-19-related topics in *ARD* during 2020, one finds almost 250 papers published either in print or online—a record number for a single subject in such a short time. About 200 of these items are correspondences and relevant responses appearing online, reflecting *ARD*'s commitment to provide an open discussion forum concerning matters of contemporary importance, but also a genuine proof of the willingness and interest of the global *ARD* readership to contribute to the topic by providing critical assessments, asking authors for additional data, sharing experience and expanding on previous communications—a true reflection of the attentiveness and strength of the readers to interact on issues related to this newly emerging disease of such global moment and societal impact.

The trajectories of this evolving information base are summarised in this first 2021 issue of *ARD* by Lauper *et al*.[11] Moreover, in the current and the subsequent 2 months, more than 9 months after the first COVID-19 publication appeared online in *ARD*, we will aggregate the online correspondences on the topic as they have evolved during the first calendar year of the pandemic so they can be easily brought into perspective by the readers.

RHEUMATOLOGISTS AT THE FOREFRONT

This pandemic was challenging for patients and rheumatologists alike. On the one hand, based on the hydroxychloroquine hype as a prophylaxis or therapy against COVID-19, further amplified by politicians but turning out to be wrong both in terms of anti-SARS-CoV-2 efficacy as well as reported major safety concerns, patients with autoimmune diseases who needed this treatment could not access it.[12] Many hospitals were overwhelmed with caring for patients with COVID-19 and had to postpone regular care. As physical distancing is extremely important in preventing infection, many patients cancelled or did not even seek appointments in doctors' offices or clinics. Consequently, other means of interaction had to be developed: virtual consultations and telemedicine rapidly expanded.[13 14] However, as was also reported in *ARD*, not seeing rheumatologists face-to-face may

bear life-threatening or organ-threatening risks.[15 16]

Beyond diseases of their immediate specialty, rheumatologists have conveyed their expertise in other respects during the pandemic. Rheumatologists are experts in immunology and its therapeutic sequelae—hardly any specialty offers the breadth and depth of knowledge about efficacy and safety of immunomodulating therapies, including biological treatments and glucocorticoids. Rheumatologists have not only been at the forefront of developing anti-inflammatory therapies for many decades,[17 18] but have also consulted for and even spearheaded trials of such therapies in patients with COVID-19, in close collaboration with pulmonologists, infectious disease specialists and epidemiologists.[19] Rheumatologists are also at the forefront of COVID-19 characterisation, for example by defining new disease entities like COVID-19-related Kawasaki-mimicking disease (Kawa-COVID-19)[20] or by caring for patients with a life-threatening cytokine storm. In this issue preliminary criteria for COVID-19 cytokine storm are presented, a potential milestone in coping with the disease.[21 22]

FROM REALITY TO VIRTUALITY AND BACK

In her ofttimes frank, honest, democratic and caring political manner, German Chancellor Angela Merkel said on the occasion of lockdown restrictions imposed to fight the pandemic in April 2020: "Diese Pandemie ist eine Zumutung für die Demokratie"—a statement full of truth and compassion; the term 'Zumutung' not easily translated confers the notion of 'imposition': 'This pandemic is an imposition on democracy'. This pandemic is also an imposition on medicine, on physicians, healthcare professionals and all involved in patient care, as it was and still is leading to despair among our colleagues in many countries. This was thoughtfully reflected in a letter on 'Hope' during the initial weeks of the pandemic, published earlier this year.[23 24] *Hopefully* the vaccines mentioned above will be soon widely available and work well, and *hopefully* effective therapies will be found.

The last year can also be regarded as the 'year of virtual congresses'. Not only was the European League Against Rheumatism (EULAR) forced to move its Annual Congress from the Frankfurt location to the virtual arena, but many national European conferences and most recently the Annual Meeting of the American College of Rheumatology were held remotely. While this format may have enabled more participants to join and likely allowed everyone to be more selective in attending sessions or talks, the lack of person-to-person and group interactions is a true loss in all the senses discussed already previously.[25] I wish the pandemic will move into virtual reality before the next Annual EULAR Congress!

BEYOND COVID-19

Let us now look beyond COVID-19 and its consequences. In this January 2021 issue a series of papers recently developed by various EULAR task forces are presented. These include the definition of difficult-to-treat rheumatoid arthritis,[26] management of adverse events elicited by immune checkpoint inhibitors[27] and prevention of fragility fractures,[28] but also deal with core sets for pregnancy registries[29] and rheumatology specialty training.[30] It is always enlightening to see the ambition and determination that govern these initiatives which provide important information based on evidence and expert opinion. In addition, points-to-consider when using Janus kinase inhibitor therapy are published[31]; of note, this paper was developed by an international task force formed across several specialties and addresses inflammatory diseases beyond the rheumatological ones.

All these papers are complemented by many original research articles on clinical and basic research efforts on rheumatological topics of major interest. And the three new sections 'Views on News', 'Heroes and Pillars of Rheumatology' and 'Thinking the Unthinkable' are all also represented this month. Please take the pleasure reading all these papers and please provide us with your feedback and suggestions.

And did you see the new appearance of *ARD?* Seven years after the previous design was introduced it was deemed desirable to change the cover of the journal. While always striving to bring cutting edge clinical and translational research into focus, the new cover reflects *ARD's* mission, with the EULAR blue brightening it up and connecting it all together. I hope that you like this new design.

All that remains now is for me to wish you a happy and healthy New Year. Please stay safe and enjoy the current and the upcoming issues of the *Annals of the Rheumatic Diseases*.

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ORCID iD
Josef S Smolen http://orcid.org/0000-0002-4302-8877

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COVID-19 cytokine storm: what is in a name?

Peter A Nigrovic [1,2]

It is now almost difficult to imagine back to a time before COVID-19 turned the world upside down. The pandemic has taken an enormous toll on patients, families and communities, working fundamental changes into our lives and into our thoughts. The medical community has formed one of many 'front lines' in the battle against COVID-19, and our lives and thoughts have been transformed as well. When the COVID-19 story is told, a key subplot will be how physicians and scientists responded to the virus. The report by Caricchio *et al*[1] in *Annals* gives us opportunity to consider the medical response to COVID-19, both at a practical level and with respect to the evolving concept of COVID-associated cytokine storm.[1]

These investigators confronted the pandemic at Temple University, in Philadelphia, one of the early epicentres of COVID-19 in the USA. In a period of 5 weeks beginning in March 2020, the Temple team admitted more than 500 adults with characteristic pulmonary ground-glass opacities, all requiring supplemental oxygen and most positive for SARS-CoV-2 by qPCR. Despite this onslaught, the team still managed to collect and analyse data to ask whether clinical or laboratory parameters accurately predicted the severe inflammatory phenotype referred to here as the 'COVID-19 cytokine storm' (COVID-CS). Lacking an accepted gold standard, the investigators employed a consensus of expert rheumatologists and pulmonologists to assign 64 patients (12%) to this category, on the basis of worsening respiratory status and elevation in C reactive protein (CRP), ferritin, D-dimer, lactate dehydrogenase (LDH), and/or troponin. COVID-CS criteria were then tested in a second cohort of 258 Temple patients admitted during a 12-day period later in April.

To develop their prediction model, they used univariate logistic regression to identify variables associated with COVID-CS and then principal components analysis to find predictors that clustered together, followed by an iterative computational algorithm to define optimal cut-off values. Ferritin and CRP did not add predictive power but were included in the final criteria per expert preference. The final model (we may call these the Temple Criteria) classified patients as COVID-CS based on (1) documented COVID-19; and (2) ferritin>250 ng/mL and CRP>4.6 mg/dL; and (3) one feature from each cluster: cluster I (low albumin, low lymphocytes, high neutrophils), and cluster II (elevated alanine aminotransferase, aspartate aminotransferase, D-dimer, LDH, troponin I), and cluster 3 (low anion gap, high chloride, high potassium, high blood ureal nitrogen:creatinine ratio). Of 513 inpatients, 173 met these criteria (34%, including 54 of the 64 gold-standard patients, sensitivity 0.84 specificity 0.73). In the validation cohort, experts considered 39 (15%) to have COVID-CS, while the criteria identified 85 (33%, including 27 of the 39 gold-standard patients, sensitivity 0.69 specificity 0.78).

Patients meeting the Temple Criteria demonstrated far less favourable outcomes. In the derivation cohort, they experienced a greater length of hospital stay (15.1 vs 5.7 days) and higher mortality (28.8% vs 6.6%), differences even more pronounced in the validation cohort (15.5 vs 4.7 days, 33.7% vs 4.2%). The case-fatality rate might have been even higher if the Temple group had not presciently employed corticosteroids at admission in all patients, well before the Randomized Evaluation of

[1]Division of Immunology, Boston Children's Hospital, Boston, Massachusetts, USA
[2]Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital, Boston, Massachusetts, USA

Correspondence to Dr Peter A Nigrovic, Division of Immunology, Boston Children's Hospital, Boston, MA 02115, USA; peter.nigrovic@childrens.harvard.edu

COVID-19 Therapy (RECOVERY) trial established this intervention as standard of care.[2]

Importantly, conventional cytokine storm scales proved poorly suited to identify COVID-CS. The 2004 haemophagocytic lymphohistocytosis (HLH) criteria, the H-Score and the 2016 macrophage activation syndrome (MAS) criteria each missed at least 75% of gold-standard patients, while classifying many others as positive. Thus, patients meeting conventional indices of cytokine storm overlapped little with those considered clinically to have COVID-CS.

Now that we have the Temple Criteria, what should we do with them? We should begin with two important caveats. First, patients in the derivation and validation cohorts were allocated to categories based on an average of laboratory values over the first 7 days of hospitalisation, or until diagnosed clinically with COVID-CS, whichever came first. As the authors note, only 43% of patients with COVID-CS met criteria at hospital admission, rising to approximately 80% by hospital day 10. Together with their imperfect sensitivity and specificity, the implication is that while the Temple Criteria can be used to assess patients at any point in time, they should be employed as a guide rather than as the sole basis to withhold (or to institute) treatment. Second, the therapeutic implications of meeting Temple Criteria remain to be established. It is tempting to conclude that patients with "COVID-CS" should be treated for cytokine storm. However, randomised controlled trials (RCTs) of interleukin (IL)-6 blockade for severe COVID-19 have proven essentially null, while an RCT of the IL-1 antagonist anakinra was halted for possible excess mortality and one testing the anti-IL-1β antibody canakinumab has just been terminated for futility.[3–5] These trials do not exclude the possibility that highly selected subsets of patients may benefit from these interventions, or that blockade of multiple immune pathways simultaneously could be more effective. However, they do leave uncertainity which additional therapies, if any, might benefit patients meeting the Temple Criteria.

This second caveat highlights the ongoing challenge of understanding what is going on with COVID-19. According to PubMed, the term 'cytokine storm' has been invoked in connection with COVID-19 by over 1000 publications. Many of these publications seem to take the idea of a COVID-CS for granted. Still, how sure are we really that severe COVID-19 is a cytokine storm?

A cytokine storm is a pathophysiologic situation in which mediators liberated by activated host cells trigger other host cells to build a self-reinforcing inflammatory spiral. Interrupting host–host signalling is an essential part of treatment. The best-understood cytokine storms arise through defects in lymphocyte-mediated control of macrophages. These syndromes result in the clinical and laboratory phenotype that HLH and MAS criteria were designed to detect, characterised by very high levels of ferritin (reflecting activated macrophages) and soluble IL-2 receptor (sIL-2R, reflecting activated lymphocytes), often in the context of high levels of IFNγ and its enabler cytokine IL-18.[6] Chimeric antigen receptor T cell-induced cytokine release syndrome (CRS) is somewhat different, mediated through antigen-directed lymphocyte activation that results in astonishing levels of IL-6; correspondingly, CRS responds to IL-6 antagonism, whereas many other cytokine storms do not.[7] However, neither acute COVID-19 nor its late manifestation multisystem inflammatory syndrome in children (MIS-C) quite mimics HLH, MAS or CRS. IL-6, ferritin, sIL-2R and IL-18 are elevated but levels remain relatively modest.[8–11] Transaminitis and cytopaenias are comparatively mild, aside from lymphopaenia that is likely a direct effect of SARS-CoV-2. Splenomegaly is largely absent. Corticosteroids do save lives, but the doses employed in RECOVERY pale in comparison with those typically required for conventional HLH, and their efficacy is not (known to be) restricted to patients meeting COVID-CS criteria. As noted, cytokine blockade in severe COVID-19 has yet to be proven effective. Although experience in selected patients treated with corticosteroids and anakinra is suggestive, these therapies are not specific for cytokine storm; further, sharp discordance between observational series and controlled trial data has been a recurring feature of this pandemic (see hydroxychloroquine, azithromycin, tocilizumab), emphasising the need for caution in the interpretation of anecdotal experience. The severe course of COVID-19 reported in individuals with defects in Toll-like receptor 7 or other interferon-related pathways, or with anti-interferon antibodies, underscores the importance of pathogen control.[12–14] Sometimes intense inflammation arises simply because an infection is overwhelming.

None of these considerations prove that COVID-19 does not unleash a cytokine storm; they simply highlight that the case remains open. In The Structure of Scientific Revolutions, Thomas Kuhn describes how scientists fit observations into an accepted explanatory paradigm until enough exceptions accumulate to put the model under stress; at that point, if a new and better model is available, a 'paradigm shift' occurs through which anomalous observations now become the foundation of a new world view. Kuhn's classic example is the shift from a Ptolemaic (Earth-centred) to a Copernican (Sun-centred) understanding of the solar system. The new model becomes the accepted paradigm until it, too, is upended by accumulating observations.[15] While our understanding of COVID-19 has not undergone revolutionary change to quite such an extent, we have still come a long way in a short time, growing to appreciate its remarkable age tropism, thrombotic risk, myocarditis, skin manifestations and (in children and some adults) delayed MIS-C presentation. As physicians struggling to come to terms with a new disease, we use familiar diseases to supply a provisional conceptual framework. This process of understanding by analogy has been hard at work in the current pandemic: COVID-19 is like other pandemic coronavirus syndromes, like CRS, like MAS, like Kawasaki disease, like toxic shock syndrome. These parallels allow us to extrapolate from what we already know but carry the risk that we may assume shared features even where evidence remains tenuous. As we apply the Temple Criteria, we must keep in mind that the term "COVID-CS" encapsulates a pathophysiologic hypothesis about how COVID-19 makes patients sick, rather than an established fact, and that data in support of cytokine storm as a frequent contributor to disease severity in COVID-19 seem to be getting weaker rather than stronger.

This concern notwithstanding, the creators of the Temple Criteria deserve our admiration for their thoughtful and persuasive investigation, conducted under the most trying of conditions. The Temple Criteria provide an important new tool to guide physicians in their evaluation of COVID-19 patients and a useful way for investigators to analyse datasets from observational and interventional trials, potentially helping to define patients who may benefit from specific interventions. They also push us to continue to think precisely about

the terms that we use and what they imply, and to remain on the alert for observations that may compel us toward the next conceptual paradigm in the COVID-19 pandemic.

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ORCID iD
Peter A Nigrovic http://orcid.org/0000-0002-2126-3702

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The role of TASL in the pathogenesis of SLE: X marks the spot

In a seminal paper published in *Nature*, Heinz *et al* provide important new information on the gene product of *CXorf21*, an X-linked gene associated with systemic lupus erythematosus (SLE).[1] Using an impressive array of molecular techniques, these investigators demonstrated that the protein encoded by a gene originally known as *CXorf21* interacts with SLC15A4, an amino acid transporter in the endolysosomal compartment; the gene for SLC15A4 has also been genetically associated with SLE. While the role of *CXorf21* in SLE had been investigated for many years, the function of its protein product was a mystery until Heinz *et al* identified it as an adaptor in TLR signalling. The name for this protein is now 'TLR adaptor interacting with endolysosomal SLC15A4' or TASL; the gene is designated as *TASL (CXorf21)*.

As the studies in THP1 and other human cells in the *Nature* paper illustrate, TASL is important for the recruitment and activation of the transcription factor IRF5 in downstream signalling by TLR 7, 8 and 9; as such, TASL has analogy with adaptor proteins like STING, MAVS and TRIF. These findings are relevant to the pathogenesis of SLE since, in this disease, DNA and RNA in the form of immune complexes can enter cells of the innate immune system to induce responses by TLR 7, 8 and 9 in the endosomes; the production of interferon and other proinflammatory cytokines is an outcome of this pathway. Interestingly, in its regulation of gene expression, TASL affects the IRF pathway but does not affect NF-κB or MAPK signalling.[1] This pattern points to a unique role of TASL in the activation of innate immunity by the endosomal TLRs (figure 1).

While the function of TASL is newly described in the paper by Heinz *et al*, the function of SLC15A4 has a longer history. The role of this protein in immune signalling was originally described in an in vivo screen in the mouse for proteins necessary for the function of plasmacytoid dendritic cells (pDCs), a key cell type for the production of type 1 interferon.[2] Among mice with defects in either pDC development or function following random mutagenesis, a strain designated as *feeble* showed aberrant production of interferon by pDCs in response to stimulation by ligands of TLR7 and 9. *Feeble* was then mapped to a mutation in *Slc15a4* which encodes a transport protein in the lysosomal compartment (the designation of these genes and proteins has varied among publications, accounting for some differences in capitalisation of the letters).

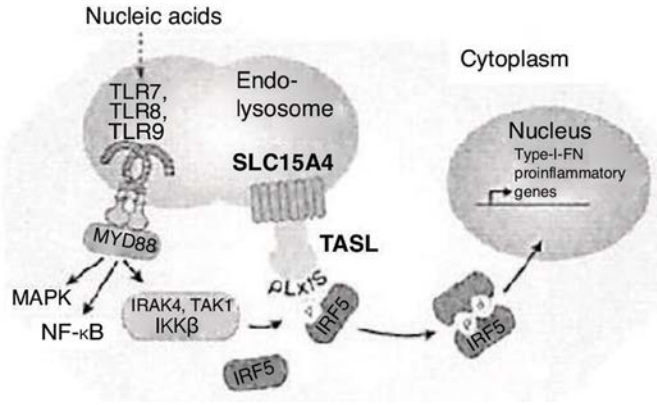

Figure 1 The role of TASL in TLR signalling. As the schematic indicates, TASL plays a key role in the activation of endosomal TLRs by nucleic acids. Following the interaction of TASL with SLC15A4, IRF5 is phosphorylated and moves to the nucleus where it promotes the expression of type 1 interferon and other proinflammatory molecules. This pathway is distinct from other endosomal TLR-dependent events, such as activation of MAPK or NF-κB (adapted from[1]).

The role of SLC15A4 in TLR signalling has now been extensively studied. SLC15A4 is a proton-coupled amino acid transporter that can move histidine and oligopeptides from inside the lysosome into the cytosol.[3] This activity is key to the creation of a subcellular environment for stimulation by TLR 7 and TLR 9 in B cells, monocytes as well as pDCs. With a loss of SLC15A4, endolysosomal pH regulation is disturbed and the production of interferon and other cytokines is reduced. In the realm of B cell responses, loss of SLC15A4 can prevent pathogenic autoantibody production. Indeed, studies on autoimmune NZB and C57BL/6-*Fas*^{lpr} mice expressing a *Slc15a4* mutant gene indicate reduced autoantibody production and other clinical manifestations of SLE.[4] Other studies using the pristane model of SLE indicated that the *Slc15a4*-/- mice have reduced production of anti-snRNP and anti-DNA, autoantibodies characteristic of SLE. SLC15A4 loss, however, does not affect the response to LPS and other TLR ligands with surface receptors.[3]

In contrast to the situation with SLC15A4, where the function of the protein was known, studies on the role of *CXorf21* primarily involved genetic approaches to explore the role of X chromosome genes.[5 6] Among the most striking findings of SLE and related diseases like Sjogren's syndrome is the strong female predominance; this number can approach 10:1. Although oestrogens and progestins have immune activity, the impact of femaleness extends beyond hormonal influences and can result from the many genes on the X chromosome related to immunity.[7] Interestingly, the more classical types of genetic studies have not shown the contribution of X-linked genes in SLE susceptibility as might be expected; this situation may reflect the more limited study of X chromosomes in GWAS studies.[6]

Elucidating the contribution of X chromosome genes in women is a challenge because of X chromosome inactivation (XCI). To balance the genetic complement of men, in women, one X chromosome undergoes XCI; this process is random and occurs in each cell to create a tissue mosaic of cells with either maternal or paternal X chromosome expression. XCI is not absolute, however, and as many as 15% of X chromosome genes can escape inactivation.[8–10] The incomplete inactivation of X chromosomes, thus, perturbs the dosage compensation of XCI and can contribute to sexual dimorphisms in responses between men and women. As many studies on humans and animals have indicated, men and women can show large differences in immune cell function affecting a wide variety of cell types.[7]

Among genes that can escape XCI is *TASL(CXorf21)*. Odhams *et al* used in silico as well as experimental approaches to establish that *TASL(CXorf21)* is an interferon responsive gene that importantly shows sexual dimorphism in its expression; immunological stimulation can further boost the level of expression.[6] Further studies by Odhams *et al* showed that the TASL protein colocalises with TLR7 in an endosomal compartment. Among susceptibility genes for SLE, *TASL(CXorf21)* is not alone in dimorphic expression. *TLR7* is another X-linked gene that can escape XCI, with overexpression leading to increased TLR7 activation by single-stranded RNA and the production of interferon.[11] The linkage between female sex, nucleic acid stimulation and interferon production is forever turning up in studies on the pathogenesis SLE.

Another system to explore the role of TASL in SLE had its origin in studies by Scofield *et al* on the occurrence of SLE in patients with X chromosome aneuploidies.[12] These investigators reasoned that, if X chromosome dosage is responsible for the increase in autoimmunity in women, then disease should show an increased prevalence

in patients with Klinefelter syndrome who are genetically XXY. Indeed, that was the case and, in a large cohort of patients, the investigative team found that the risk of SLE is increased approximately 14-fold compared with men who are XY.[12]

Subsequent studies by these investigators focused on *CXorf21* because it can escape XCI and, like *TLR7*, has risk alleles; the CXorf21 protein is also expressed in an endolysosomal compartment where TLR signalling occurs.[13 14] These studies demonstrated that knockout of *CXorf21* in monocytes by CRISPR-Cas9 transfection affected lysosomal pH; other data showed that lysosomal pH in 46XX women who exhibit overexpression of CX*orf*21 in cells such as monocytes, B cells and dendritic cells is more acidic than that of similar cells in men. While differences in lysosomal acidification can affect TLR signalling, it can also affect antigen processing; these findings suggest that female-male differences in immune responses may reflect a number of different mechanisms and not simply cytokine production by TLR stimulation. In this regard, the mechanisms by which TASL and SLC15A4 regulate endolysosomal pH are unknown and will require further investigation.

The identification of TASL as an adaptor is an important finding that must be incorporated into an emerging picture of the regulatory interactions in the endolysosomal compartment and the interplay between acidification and signal transduction via IRF5. Of course, the efficacy of hydroxychloroquine (HCQ) in the treatment of SLE fits well into this scheme since at least one of this drug's actions is to reduce lysosomal acidification; as a base, HCQ that can accumulate in lysosomes. It would be interesting to explore the effects of HCQ in men with SLE since the higher pH on their lysosomes may suggest diminished efficacy of an approach to increase their pH.

The differences between men and women is one of the most fascinating subjects in biology and is essential for developing personalised medicine approaches to treat disease.[7] Unlike other conditions where male-female prevalences may be more similar, in SLE, the overwhelming predominance of women makes a study of male-female differences in treatment responses both more difficult and seemingly less pressing. Nevertheless, a comparison between male and female biology is always insightful and could shed new light on events in SLE; interestingly, one study suggested that immunologists may give less attention to comparing biological responses of men and women than investigators in other fields, a surprising finding in view of the great interest in diseases such as SLE.[15]

Because of the predominance of women with autoimmunity, the field has a tendency to look at sex differences through the lens of pathology (ie, autoimmunity), emphasising how proteins like TASL can promote deleterious cytokine production. On the other hand, women can mount much more effective antibody responses than men and have improved outcomes in many infections. While determination of outcomes in COVID-19 infection is complicated because of race, socioeconomic status and comorbidities, men appear at greater risk than women; the same was true with the 1918 influenza pandemic.[16] In understanding male-female differences in SLE and other immune-mediated conditions, the identification of the protein product of *CXorf21* as TASL is a major step and emphasises that, in the search for chromosomes where susceptibility genes for autoimmunity may be located, X marks the spot.

David S Pisetsky [1,2]

[1]Departments of Medicine and Immunology, Duke University Medical Center, Durham, NC, USA
[2]Medical Research Service, Veterans Administration Medical Center, Durham, NC, USA

Correspondence to Dr David S Pisetsky, Departments of Medicine and Immunology, Duke University Medical Center, Durham, NC 27705, USA; david.pisetsky@duke.edu

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ORCID iD
David S Pisetsky http://orcid.org/0000-0002-3539-5351

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Jan Mikulicz-Radecki (1850–1905): return of the surgeon

Bernhard Manger , Georg Schett

Handling editor Josef S Smolen

Department of Medicine 3, Friedrich-Alexander-University Erlangen-Nuremberg and Universitätsklinikum Erlangen, Erlangen, Germany

Correspondence to
Professor Bernhard Manger, Universität Erlangen-Nürnberg, Erlangen 91054, Germany; Bernhard.Manger@uk-erlangen.de

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A medical eponym honours a scientist's accomplishment in discovering a disease, symptom, anatomical part, procedure or principle.[1] Many of them are firmly embedded in our terminology, such as Hodgkin's disease, Babinski's sign, Meckel's diverticulum or Billroth's surgery, respectively. Eponyms can be very helpful for professional communication, because they evoke characteristic images in every medical student or doctor and are usually easier to memorise than designations based on pathophysiology or their acronyms. However, the use of eponyms also has disadvantages. They may become outdated, because a progress in knowledge requires a new terminology, or worse, the name belongs to a person, whose acts or views are not in accordance with the social ethos of medical literature.[1 2] Therefore, many medical eponyms that once were popular have become outdated over the course of time. In rheumatology, we are currently witnessing a rare phenomenon: an eponymous designation for a disease, which 100 years ago was frequently used in the literature, then became almost forgotten and now reappears in the context of a new immunopathology: 'Mikulicz's syndrome'.

Jan Mikulicz-Radecki (from 1899 Johann Freiherr von Mikulicz-Radecki) was born in 1850 in Černivci (then part of the Austro-Hungarian Empire, today Ukraine) as son of a Polish forest and construction official (figure 1). Initially pursuing a career in music, he began his medical training at the University of Vienna in 1869. After finishing his studies in 1875, he became voluntary assistant and later a close friend of the famous surgeon Theodor Billroth. Mikulicz's contributions to surgery are numerous. He was the first to perform endoscopies of oesophagus and stomach and described achalasia as sphincter dysfunction. He created new techniques for operations in various areas of the body, such as partial thyroidectomy, lateral pharyngotomy, maxillary sinus drainage, ileocystoplasty and pyloroplasty, the latter still named Heineke-Mikulicz method. His postdoctoral thesis, earning him the title of a lecturer in surgery, covered yet another discipline, orthopaedics, 'About the genu varum and valgum', with the first description of the weight bearing Miculicz line.[3 4] In addition, he fathered numerous inventions such as a device for ether anaesthesia, a heated operation table, a special forceps and various other instruments. When he received a scholarship for a scientific trip to several European universities, he became acquainted with Joseph Lister's new concept of antisepsis in London, which he adopted vigorously and became the first doctor in the world to wear operating gloves.[5] Mikulicz was fluent in Polish, Ukrainian, Russian, English and German, but when asked about his nationality, he answered: 'I am a surgeon.'[6] In 1882, Mikulicz moved to Kraków, to become Head of the Department of Surgery at the prestigious Jagiellonian University, where he continued to build his reputation as an excellent physician and researcher. In January 1888, briefly after taking over the Chair of Surgery at the Prussian Albertus-University of Königsberg (Kaliningrad), Mikulicz presented a patient with 'multiple swellings involving salivary and related glands' to the members of the local Society for Scientific Medicine.[7]

In 1890, he moved again to become Head of Surgery at the University of Breslau (Wrocław), where he created the most modern operating room in Europe at that time. There, he also performed the first thoracotomy in a low-pressure chamber together with his protégé Ferdinand Sauerbruch.[8] It took until 1892, when he finally got around to publish his earlier observed case in a special edition to honour his teacher Theodor Billroth.[9] In it, he describes the detailed history of a 42-year-old farmer with massive, symmetric, painless and permanent swelling of all lacrimal and salivary glands, without any signs of systemic manifestations. It is of interest that he notes 'ample' secretion of saliva during examination and on stimulation with pilocarpine. After removal of both submandibular and lacrimal glands, he observed a preserved lobular structure despite their increased size. Microscopically, he describes a massive infiltration with small round cells around intact secretory acini and compares the appearance to 'lymphadenoïd tissue' taking great effort to separate this from malignant infiltration (figure 2). A reprint and English translation of his original paper appeared in the 'Medical Classics' series.[10]

Despite the fact that almost simultaneously, the Viennese ophthalmologist Ernst Fuchs published a very similar case[11] and both scientists quote each other's observations, only one name became associated with the new disease. In the years to follow, reports of 'Mikulicz's disease' flooded the literature and created a lot of confusion. Some authors suggested separating a benign form of 'Mikulicz disease proper' from 'Mikulicz's syndrome', just describing glandular involvement in leukaemia, tuberculosis or other systemic diseases.[12 13] In 1908, yet another type of glandular infiltration was described by Christian Frederik Heerfordt in Kopenhagen.[14] This form of parotitis associated with uveitis and facial palsy was many years later identified as part of the spectrum of Boeck's sarcoidosis.[15]

Figure 1 Jan Mikulicz-Radecki (1850–1905), Author unknown, Wikimedia commons (https://commons.wikimedia.org/w/index.php?curid=8348730).

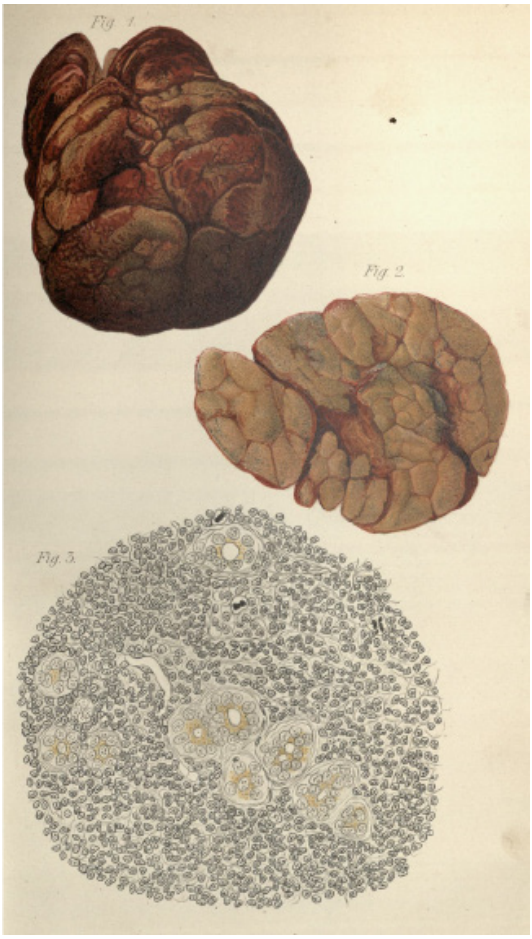

Figure 2 Colour print of a drawing from Mikulicz's original publication showing gross anatomy and histopathology (saponin staining) of the left submandibular gland.[9]

The greatest confusion, however, was yet to arrive, when Henrik Sjögren published his paper about 'Keratoconjunctivitis sicca' in 1933. The ophthalmologist Sjögren, who focused his work almost entirely on xerophthalmia and corneal lesions, did not at all intend this. He reported no lacrimal gland swelling in his patients, nor he did he refer to Mikulicz's earlier work at all.[16] Nevertheless, over the following 50 years, the debate continued, whether Mikulicz's disease and Sjögren's syndrome were different diseases or part of the same spectrum.[12 17] The elimination of either term[17 18] or a combination of both[19] was suggested. But over time and with the availability of Ro(SS-A) and La(SS-B) autoantibodies, Sjögren's syndrome became the preferred terminology. Towards the end of the 20th century, Mikulicz's name had almost completely disappeared, at least from rheumatology textbooks.[20]

The resurrection of this eponym started with the discovery of IgG4-related disease (IgG4-RD) as a new entity with a unique pathophysiology in 2001. Next to pancreatic and retroperitoneal tissue infiltration, lacrimal and salivary glands are the most frequently involved organs in this systemic disorder. In retrospect, the clinical characteristics of IgG4-related glandular disease with its permanent indolent swelling and only mild or absent secretory dysfunction is much more consistent with Mikulicz's original description than with Sjögren's. Therefore, we are currently witnessing the comeback of the eponym 'Mikulicz' in the context of IgG4-related gland involvement, which can clearly be separated from Sjögren's syndrome on demographic, clinical, serological and immunohistochemical grounds.[21 22] In a recent multinational effort to cluster clinical subtypes of IgG4-RD, about one quarter of all patients presented with a distinct phenotype, which was labelled 'Mikulicz syndrome and systemic'.[23]

Finally, yet another mystery may be solved by interpreting Mikulicz's observations as the first report of IgG4-RD. In his paper, he describes that his patient initially did well after removal of lacrimal and submandibular glands, but only 3 months later died from unexplained 'peritonitis (perityphlitis?)'.[9] In modern publications, involvement of the appendix has occasionally been reported as a complication of IgG4-RD.[24 25] Almost 130 years after Mikulicz's original publication, its last sentence still holds true: 'I hope that future observers will succeed in solving the riddle which this remarkable disease presents to us.'[10]

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ORCID iDs
Bernhard Manger http://orcid.org/0000-0003-2375-0069
Georg Schett http://orcid.org/0000-0001-8740-9615

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Publishing in 2@84

Marco Lanzillotta ,[1,2] Chiara Crotti,[3] Vital Manuel Da Silva Domingues,[4,5] Kim Lauper ,[6] Gerd R Burmester[7]

Handling editor Josef S Smolen

[1]Università Vita-Salute San Raffaele, Milano, Lombardia, Italy
[2]Unit of Immunology, Rheumatology, Allergy, and Rare Diseases, UNIRAR, San Raffaele Scientific Institute, Ospedale San Raffaele, Milano, Lombardia, Italy
[3]Department of Rheumatology, ASST Gaetano Pini-CTO, Milan, Italy, Milan, Italy
[4]Hospital Santo António - Unidade Medicina B, Instituto Ciências Biomédicas Abel Salazar, Porto, Localidade, Portugal
[5]Instituto Gulbenkian de Ciencia, Oeiras
[6]Department of medicial specialities, University Hospitals of Geneva, Geneva, Switzerland
[7]Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, Germany

Correspondence to
Dr Marco Lanzillotta, Università Vita-Salute San Raffaele, School of Medicine; Unit of Immunology, Rheumatology, Allergy, and Rare Diseases, San Raffaele Scientific Institute, Ospedale San Raffaele, 20132 Milano, Lombardia, Italy; lanzillotta.marco@hsr.it

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This article arose within the framework of the EMEUNET peer review mentoring program.[1] This project allows mentees to independently review articles submitted to Annals of the Rheumatic Diseases and RMD Open, tutored by an expert reviewer, thus nurturing their critical skills in the interpretation of a paper. After reviewing several papers together, the authors of this manuscript concluded the program fantasising about the potential changes in the editorial processes in the near and not so near future, resulting in this brief story. In particular, the authors thought about the delicate role of reviewers and editors, whose intellectual independence and integrity represent the foundation of the peer-review process.

We take you into the year 2@84 and describe the last day of work of Professor Ned, the editor of Rheumacity, the global comprehensive rheumatology knowledge database. He now must now handover his tasks to Highly Automated Logic Editor (HAL-E), the recently developed artificial intelligence and future editor in chief of Rheumacity, who is of course no longer a human being. While in his home and performing the final tasks in this handover to the machine, he recapitulate show he started his career in this field, how publishing evolved, what can go wrong and what the future will bring. He is a human and his mind is rambling on his last day at work.

Professor Ned's last day at Rheumacity

…Ned woke up at one of the hottest dawn of the summer, looking for his near-sightedness spectacles and a glass of water on the bedside table. The thirst quencher was waiting there, close to a new generation tablet and the touch free lamp. He took this habit from his old grandpa. 'Always keep a glass of water on your nightstand, and a book. They both will make you sleep better.' A book, what an odd name. The black ink on the printed paper was so old-fashioned, with an even medieval scent. Ned smiled recalling the naïve gesture of his grandpa smelling the paper. How was it like? Ned could not recall that woody and cosy smell. Books had disappeared from the editorial world many years ago, while he was learning to read on tablets. There were still some museums harbouring these antique treasures.

Despite a subtle nostalgia, he approved that. Forests were being destroyed, and there was no more room for paper production for leisure. The golden age of books belonged to the past when indisputable goals were reached. Indeed, the great Library of Alexandria had acquired almost 700 000 papyrus scrolls at its climax, reflecting the ambitious project aimed at storing all the available literature. Interestingly, papyrus scrolls had a short physical half-life and copies had had to be made constantly in order to save the knowledge. Obviously, there had been no cloud storage at that time and many scrolls had been destroyed by moisture and fire (https://www.sueddeutsche.de/kultur/bibliothek-alexandria-aegypten-antike-caesar-papyrus-islam-pharaonen-1.4232218, accessed 15 September 2020). More than a thousand years later, Diderot had tried to condensate all the world knowledge into the *Encyclopédie*. Twenty-eight volumes had been published between 1751 and 1772. What would Diderot think, seeing his greatest endeavour now stored in flash drive of less than 1-inch length?

Ned was happy that words and information could now be conveyed in portable devices or downloaded from the cloud and read on a High Definition screen, perhaps even better than on paper. This unprecedented change was embraced by the entire editorial world, even by scientists, especially by scientists.

Looking back into the beginning of his career, he realised that he had not yet earned his MD degree at the time of the Great Scientists Rebellion (GSR), an event that had marked the disruption in the editorial field, still vivid in his memories. At that time, the slogan '*payin' for publish, publish for citin*'' had been popping in his mind every now and then. The past must have been a hard stage for a young scientist! Older colleagues had been in the habit to repeat like a mantra '*publish, get cited or perish*', but nobody was used to highlight the actual cost of getting published and the role of citations and autocitations have never been deeply questioned. '*Stuff your paper with your citations*!' had the seniors advised in confidential discussions. What was the role for that other than artificially inflating the authors' ego, H index, and perceived importance? *Occasio facit furem,* grinned Ned, envisioning a future in which the upcoming editorial progresses would wipe out the old purported meritocratic façade.

After mulling over these considerations, Ned reached the workplace, downstairs. It was his last day at *Rheumacity*, how bittersweet! In his career, after a solid experience as a researcher in a tertiary care centre, he had taken an opportunity as a trainee editor in the field of rheumatology, receiving a quick introduction to the latest advances in editorial management and had soon become a point of reference in the field. However, progress moved even faster than his bright career, making his job old-fashioned and his role replaceable. Indeed, the GSR had marked a watershed with the old world. In this brave new world, there were

no scientific journals and even no papers! Only concepts and experiments, both from clinical and basic research that were constantly uploaded in the *Rheumacloud*, the online server. Of course, none of the old medieval boundaries were present, and the material was available to everybody, for free. Moreover, without filters. Randomised controlled trials together with case reports, all populating the net of Rheumacity, waiting for being viewed, commented and downloaded. The items that received the greatest attention from the visitors were shown in the foreground, in a very democratic and fair way.[2–5]

His role had deeply changed over the last few years. He just needed to enter the newly formed Rheumacity, the virtual reality where all rheumatic diseases-related topics were uploaded, and take a census of the daily uploaded content, counting the contributions, but without providing any filter. There was no role for that any longer. After all, how can a censor discriminate whether a concept or an experiment is meaningful or not? The community of web surfers could surely perform this task better and in an unbiased way, well deciphering and interpreting this blog-based literature. Despite huge advances in storage technology, cloud memory was not unlimited, therefore, Ned's tasks had included the removal of the less viewed items—an action performed on a regular basis and helped by respective algorithms. How many nice articles had disappeared just because they did not meet the favour of the most, *like tears in rain*! He had felt like a web gardener, trimming and nurturing the existing knowledge, but without interfering with it. A noble role, a sort of modern guardian. Yet, now artificial intelligence could perform this task better and faster, he acknowledged. 'That's why I have to retire now', concluded Ned, somehow welcoming this change for the sake of a better, more democratic and functional social-based scientific literature.

Yet, not all glitter is gold. Few but severe issues had occurred since the foundation of Rheumacity. First, right after the activation of the online servers, a violent hacker attack took place. The so-called web pirates damaged Rheumacity by uploading a yottabite of content, thus paralysing the web. Ned's older colleagues had had hard times in restoring the order. The villains had never been found, but evidence pointed toward an obscure sect, the Ethycalists, born after the GSR. The members of the Ethycalists had fiercely disapproved the modern blog-based scientific literature, especially for the (perceived) little attention given to the informed consent and patient's privacy, often sacrificed for the sake of global knowledge and of progress.

A few years later, an incredibly high solar activity had shut the servers down for a whole week,[6] the 'Blank Week', as it was later termed. The Blank Week not only affected Rheumacity but had hit all fields! Actually, Cardiocity reported the greatest damage. Some of the contents had been totally wiped out and editors had had to go back to the archives to restore them. Yet, some rumours had it that not everything had been recovered since materials stowed in older devices, like universal serial bus (UBS) pens—or was it USB?, he cannot even remember the name!—had not been accessible anymore.

Ned often found himself thinking about the pros and cons of this editorial evolution. Despite the above-mentioned turndowns, he deeply thought that a change in academic publishing was required. There had been hints everywhere since the beginning of the century! When humankind was threatened during the first great SARS-CoV-2 pandemic, doctors and scientists had exchanged vital information through social media or had shared via preprints new treatment protocols even prior to a formal review process. Moreover, the reviewing process itself had been made faster to provide the latest news to healthcare practitioners in order to overcome this new enemy. Last, but not least, given the global burden of the disease, all the publications related to the topic had been made open access, meaning that no fees nor subscriptions had been required to view or download them. All these changes had acted as a powerful boost towards the current situation. On the other side, critics had claimed that the consequences of these virtuous actions had been detrimental, flooding the scientific literature with low-quality data leading to confusion and mistakes, both in the scientific community and general public. Reviewers had acted as presumably innocent bystanders, being forced to review an increased volume of articles in lesser time, often at the expense of quality. This concept had been magnificently crystallised even earlier, with the word 'Infodemiology',[7] a new discipline that 'identifies areas where there is a knowledge translation gap between best evidence (what some experts know) and practice (what most people do or believe)[8] ', ultimately providing quality health information on the Internet. In the infodemic era, real-time science helps to share knowledge through the world in a matter of seconds, but facts and discoveries shall be referred as Best Evidence at the Time and must be further tested and confirmed or retracted.[8]

Ned no longer has a place in this ever-changing infodemic world. As an editor of Rheumacity, he was asked to visualise all the uploaded contents, distributing proper tags according to topics and trends. These actions are required to provide a basic, but solid frame, without which the articles related to different fields would be inevitably be mixed one after the other. But then the ball shifted to the info(/)deemers who view, rate, and comment each item. In this context, Ned is aware that his role and expertise are now obsolete, being easily overcome by computers, which outperform him in many ways. Therefore, for his faith in progress, he agreed to step aside and resign in favour of a Highly Automated Logic Editor, the recently developed artificial intelligence and future editor in chief of Rheumacity. This mythical handover between men and machines would take place at the end of the day, marking a point of no return in the scientific world.

As technology is progressing and storage capacity dramatically increases on a yearly base, free memory will not be an issue anymore. Data will be displayed on a most viewed—most will view fashion, being exclusively modelled by the clicks and comments of the web-surfers in an autonomous, unbiased, yet uncontrollable way.[9]

…We hope that this naïve vignette will prompt the reader to reflect on this challenging topic. Like Ned, we acknowledge that caveats exist in the current peer-review process, in which the limit between a 'we are delighted to inform…' and 'we regret to…' might not always be objective, and article's publication can depend on fee payment. Yet, the 'magnificent and progressive fate'[10] welcomed by Ned, in whom everything is uncontrolled and uncontrollable for the sake of a greater good might rather lead toward a dystopian reality, devoid of the critical and inspiring insights provided by reviewers.

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ORCID iDs
Marco Lanzillotta http://orcid.org/0000-0002-4522-2921
Kim Lauper http://orcid.org/0000-0002-4315-9009

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Update on the diagnosis and management of systemic lupus erythematosus

Antonis Fanouriakis [1], Nikolaos Tziolos,[2] George Bertsias [3,4], Dimitrios T Boumpas [2,5,6,7]

Handling editor Josef S Smolen

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[1]Department of Rheumatology, "Asklepieion" General Hospital, Athens, Greece
[2]4th Department of Internal Medicine, "Attikon" University Hospital, Athens, Greece
[3]Rheumatology, Clinical Immunology and Allergy, University of Crete School of Medicine, Iraklio, Crete, Greece
[4]Laboratory of Autoimmunity-Inflammation, Institute of Molecular Biology and Biotechnology, Heraklion, Crete, Greece
[5]Joint Rheumatology Program, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[6]Medical School, University of Cyprus, Nicosia, Cyprus
[7]Laboratory of Autoimmunity and Inflammation, Biomedical Research Foundation of the Academy of Athens, Athens, Cyprus

Correspondence to
Dr Dimitrios T Boumpas, 4th Department of Internal Medicine, "Attikon" University Hospital, Athens 124 62, Greece; boumpasd@uoc.gr

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ABSTRACT

Clinical heterogeneity, unpredictable course and flares are characteristics of systemic lupus erythematosus (SLE). Although SLE is—by and large—a systemic disease, occasionally it can be organ-dominant, posing diagnostic challenges. To date, diagnosis of SLE remains clinical with a few cases being negative for serologic tests. Diagnostic criteria are not available and classification criteria are often used for diagnosis, yet with significant caveats. Newer sets of criteria (European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) 2019) enable earlier and more accurate classification of SLE. Several disease endotypes have been recognised over the years. There is increased recognition of milder cases at presentation, but almost half of them progress overtime to more severe disease. Approximately 70% of patients follow a relapsing-remitting course, the remaining divided equally between a prolonged remission and a persistently active disease. Treatment goals include long-term patient survival, prevention of flares and organ damage, and optimisation of health-related quality of life. For organ-threatening or life-threatening SLE, treatment usually includes an initial period of high-intensity immunosuppressive therapy to control disease activity, followed by a longer period of less intensive therapy to consolidate response and prevent relapses. Management of disease-related and treatment-related comorbidities, especially infections and atherosclerosis, is of paramount importance. New disease-modifying conventional and biologic agents—used alone, in combination or sequentially—have improved rates of achieving both short-term and long-term treatment goals, including minimisation of glucocorticoid use.

SLE: A CHALLENGING DISEASE WITH A FASCINATING CHRONICLE

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease of variable severity and course, characterised by a tendency for flare (figure 1).[1] In SLE, both innate and adaptive immune responses are involved. Interaction of genes with environmental factors leads to numerous immunologic alterations that culminate into persistent immune responses against autologous nucleic acids. Tissue damage—caused by autoantibodies or immune-complex depositions—occurs in kidneys, heart, vessels, central nervous system, skin, lungs, muscles and joints leading to significant morbidity and increased mortality.[1]

The chronicle of lupus in the stream of medical history is fascinating.[2–4] Hippocrates (460–375 BC) may have first described the disease, calling it *herpes esthiomenos* (*ἕρπης ἐσθιόμενος*) or 'gnawing dermatosis'. Herbernus of Tours applied the term *lupus* to a skin disease in 916 AD. In 1872, Kaposi subdivided lupus into the *discoid* and *systemic*, introducing the concept of systemic disease with a potentially fatal outcome.

Major milestones in the history of SLE include the description of the lupus erythematosus cell; the appreciation of its familial aggregation; the recognition of the lack of a typical disease pattern and the need to consider the overall picture for its diagnosis; and the discovery of the New Zealand Black/New Zealand White F1 lupus mouse model. In 1954, hydralazine-induced lupus was described and in 1982 the ACR classification criteria for SLE were published. During 1964–1990, the treatment of severe SLE with high doses of glucocorticoids and immunosuppressive/cytotoxic drugs was introduced. In 2011, the first biologic therapy for SLE (belimumab, Benlysta) was approved.

In this update, we are discussing evolving concepts in SLE. Of necessity, this is not a comprehensive review. We discuss selected studies—most published within the last 5 years—highlighting their impact on the field and the care of lupus patients. At the same time, through the extensive use of Tables, Figures, Algorithms and Boxes, we provide practical, easy to use information for its management.

EPIDEMIOLOGY AND CAUSES

Epidemiology and burden: milder cases in community-based registries but progression over time

SLE has a striking female predominance, with almost 10 women patients for every man affected by the disease. Incidence ranges between 0.3–31.5 cases per 100 000 individuals per year and has increased in the last 40 years, probably due to recognition of milder cases. Adjusted prevalence rates worldwide are approaching or even exceeding 50–100 per 100 000 adults.[5] In community-based Caucasian registries, most patients are middle-aged women and approximately 50% of cases are mild at presentation (figure 2A).[5] However, a proportion of patients may progress in severity, so that mild, moderate and severe cases are equally split over time to one-third in each category (figure 2B).[5 6] Disease severity may vary according to ethnic background and is generally worse in patients of African ancestry and Latin Americans. Health-related quality of life is greatly compromised.[7] Annual direct (health care-related) costs are highly related to the severity of the disease and organ(s) involved[8] and are estimated to be at least US$3000–12 000 in

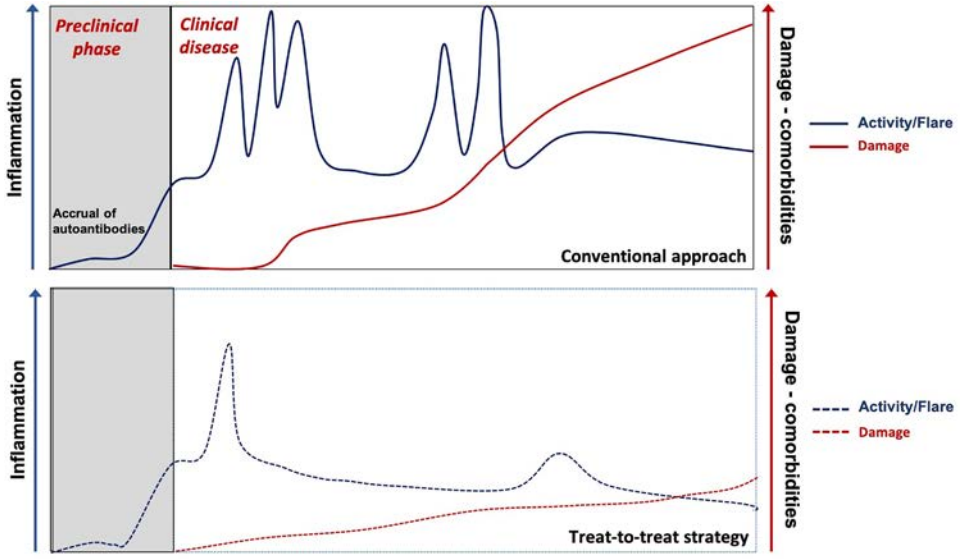

Figure 1 Natural history of SLE and the potential impact of a treat-to-target strategy. The disease starts with a preclinical, asymptomatic phase characterised initially by the appearance of autoantibodies common to all autoimmune diseases and, later, of lupus-specific autoantibodies. Subsequent clinical course is characterised by periods of variable disease activity (measured by SLE disease activity indices), with frequent flares resulting in inflammation-driven irreversible damage. Damage—measured by the SLICC/ACR damage index—increases the morbidity and mortality in SLE. Damage is driven initially by inflammation and later—with progression of the disease—also by therapy. With time, comorbidities such as infections, premature atherosclerosis and malignancies become an important part of the disease burden. Effective therapy targeting low-disease activity or remission has the potential to decrease the frequency and severity of lupus flares and resulting damage. ACR, American College of Rheumatology; SLE, systemic lupus erythematosus.

the USA and €2500–5000 in Europe for patients with moderate to severe disease.[8–10]

Environmental factors, heritability and co-segregation with other autoimmune diseases

Ultraviolet radiation, smoking and drugs are well-established environmental factors linked to SLE pathogenesis.[1] At least 118 drugs have been associated with induced lupus, particularly procainamide and hydralazine, while anti-tumour necrosis factor agents (infliximab, adalimumab, etanercept) have been linked to anti-DNA antibody production.[11] Among all lupus-related autoantibodies, antiphospholipid (aPL) and anti-DNA antibodies have been associated with smoking.[12 13]

In general, a polygenic additive model with familial aggregation of SLE cases and also with other autoimmune diseases has been recognised. In a nation-wide study from Taiwan, the relative risks (RRs) for SLE were 315.9 for twins of patients with SLE, 23.7 for siblings, 11.4 for parents, 14.4 for offspring and 4.4 for spouses without genetic similarity.[14] The concordance of SLE in monozygotic twins has been estimated to be around

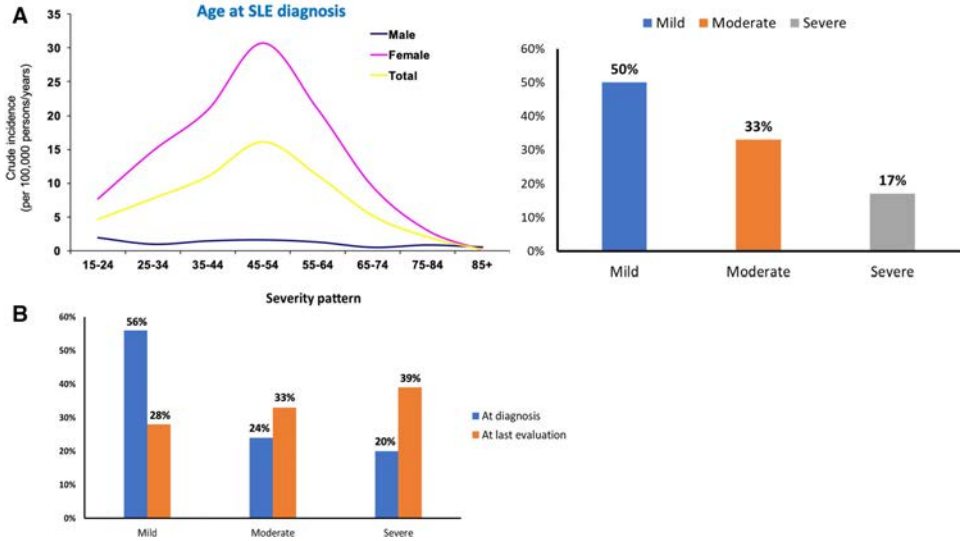

Figure 2 (A) Prevalence and disease severity in SLE. In community-based registries, most patients are middle-aged women and approximately 50% of cases have a mild disease at presentation. In contrast, in tertiary referral centres, most cases have moderate or severe disease. Data from Gergianaki *et al*.[5] (B) Disease progression in SLE. Although most patients with SLE initially present with mild disease, a proportion may progress in severity, so that mild, moderate and severe cases are equally split over time to one-third in each category. Data from Nikolopoulos *et al*.[6] SLE, systemic lupus erythematosus.

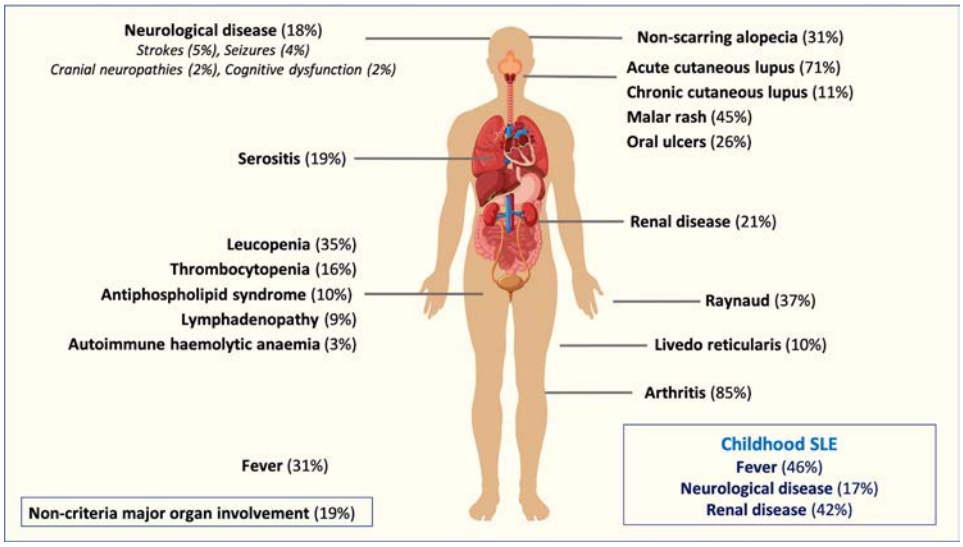

Figure 3 Key features and organs involved in SLE. Cumulative frequencies are depicted. Of note, the frequency of nephritis is not as common as previously reported, which may have been the result of referral biases in major lupus centres. Neuropsychiatric disease is an emerging frontier in lupus care. Childhood SLE has higher activity at presentation, is more likely to be severe and to receive more aggressive therapy, as well as accumulate damage. Data from Nikolopoulos *et al*.[18] SLE, systemic lupus erythematosus.

25%.[15 16] Genetically determined heritability was calculated at 43.9%, whereas shared ('familial') and non-shared environmental factors accounted for 25.8% and 30.3% of SLE susceptibility, respectively. RRs in individuals with a first-degree relative with SLE for various autoimmune diseases vary from 5.87 for primary Sjögren's syndrome (SS), 5.40 for systemic sclerosis, 2.95 for myasthenia gravis, 2.77 for inflammatory myositis, 2.66 for rheumatoid arthritis (RA), 2.58 for multiple sclerosis, 1.68 for type 1 diabetes mellitus, 1.39 for inflammatory bowel diseases, to 0.86 for vasculitis; these data can provide useful guiding information in counselling families with affected members and provide a basis for understanding the association (or lack of) with other autoimmune diseases. The familial aggregation of primary SS, SLE and RA has been delineated by use of whole-exome sequencing in 31 families with autoimmune rheumatic diseases; rare genetic variations in T-cell receptor signalling pathway seem to be the common denominator for this aggregation.[17]

ALL LUPUS PHENOTYPES: 'GREAT AND SMALL'

Diagnosis of SLE and the confusion with classification versus diagnosis; 'choosing wisely' in SLE

Key disease features and their frequency at disease onset and cumulatively can be found in figure 3.[18] Diagnosis can be challenging in (1) early stages of the disease, when a limited number of features may be present; (2) antinuclear antibody (ANA)-negative cases or organ-dominant forms and (3) rare disease presentations, which can nonetheless be severe and require prompt treatment. In our experience, non-rheumatologists fail to look consistently for arthritis and to take into consideration features of the disease not present simultaneously. A negative ANA test cannot rule out SLE diagnosis, because up to 20% of patients may be negative (true or false negative) at various stages of the disease, although typically the rate of ANA-negative lupus is much lower.[19] Other 'unwise choices' include (a) repeating of ANA testing (if once positive), (b) frequent testing of serology in patients with steadily improving or inactive disease and (c) omitting urinalysis from the routine laboratory check. Similar to other chronic diseases, physicians often fail to rule out non-lupus-related causes when trying to explain patient symptoms, with the tendency to attribute them to lupus. Among the many mimics of SLE, viral infections or parasitic infections such as leishmaniasis and lymphoid malignancies need to be considered and excluded.[20]

The diagnosis of SLE is clinical, supported by laboratory investigation indicative of immune reactivity or inflammation in various organs. Newer sets of classification criteria[21–23] enable the earlier classification of SLE, with the combination of all three sets (ACR-1997, SLICC-2012 and EULAR/ACR-2019) ensuring the capturing of non-overlapping groups of patients (although at the expense of reduced specificity).[18] ANA or other immunologic positivity (autoantibodies or hypocomplementemia) are required for classification of SLE according to the SLICC-2012 and EULAR/ACR-2019, but not the ACR-1997 criteria. Fulfilment of the classification criteria is not necessary for the diagnosis for SLE. In patients with early disease, the SLICC and EULAR/ACR are more sensitive than the ACR, while the EULAR/ACR criteria have superior specificity. In spite of this superb performance, some patients with potentially severe disease can still be missed. Modification of the classification criteria may enhance their sensitivity, allowing earlier diagnosis and treatment of more patients with high disease burden (figure 4).[24 25]

Endotypes and organ dominant lupus

Among the various endotypes, childhood-onset SLE (cSLE), organ-dominant SLE (dermatologic, musculoskeletal—so called 'rhupus'—, renal, neurological, haematologic), lupus with antiphospholipid syndrome (APS) and SS have received more attention due to differences in prognosis and treatment (online supplemental figure S1). cSLE has higher activity at presentation and is more likely to be severe and to receive more aggressive therapy, as well as accumulate damage. The presence of APS increases the risk of neuropsychiatric SLE (NPSLE), thrombotic and obstetric complications.[1] In our experience, up to one-third of patients with apparent primary APS can manifest lupus-like features. Similarly, patients with presumed idiopathic thrombocytopenic purpura, haemolytic anaemia, serositis, APS or SS

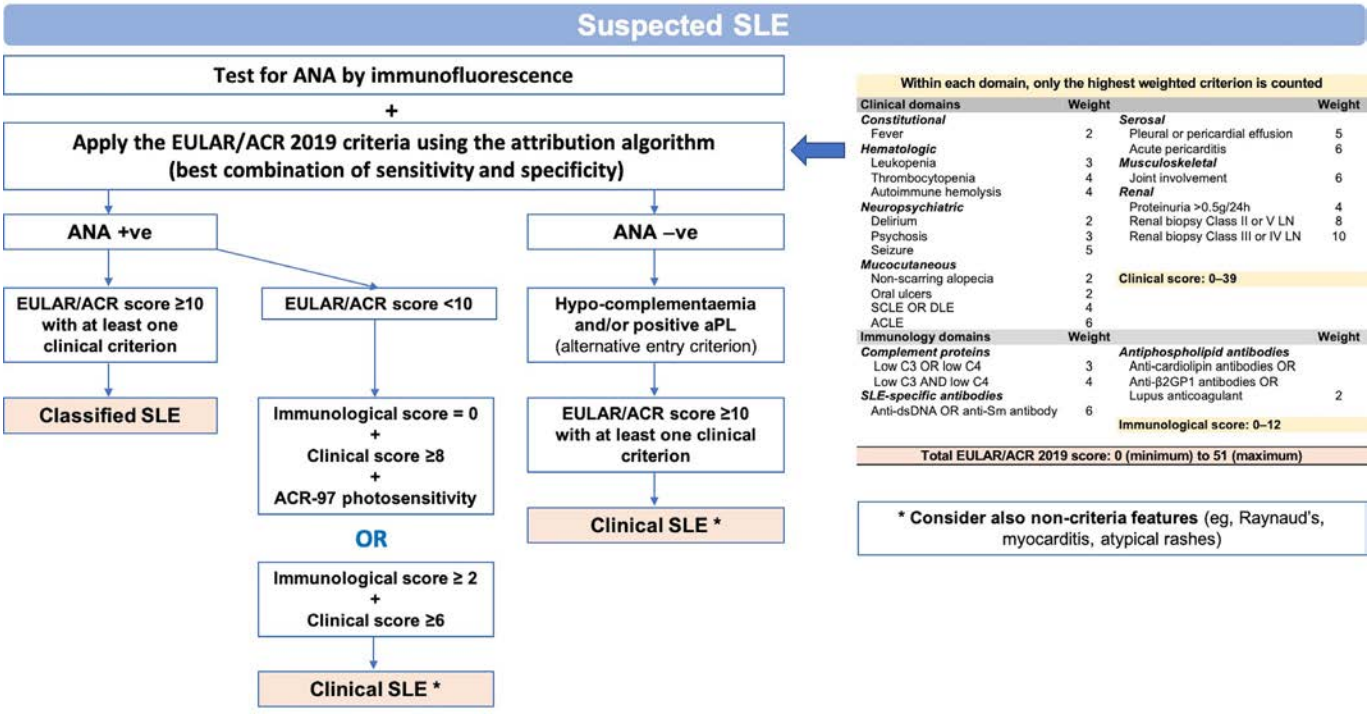

Figure 4 Diagnostic approach to a patient with suspected SLE and the use of classification criteria to aid clinical diagnosis. The diagnosis of SLE is clinical, supported by laboratory abnormalities including serologic assays. Diagnostic criteria are not available for SLE and classification criteria are often used as such, but with several caveats. Among classification criteria, the EULAR/ACR-2019 have the best combination of sensitivity and specificity but require positive ANA as an entry criterion. However, for diagnosis, some patients may be ANA-negative; in such cases, low complement levels and/or positive anti-phospholipid antibodies could be used as an alternative entry criterion in the classification algorithm. For patients who fall short of the classification threshold (ie, EULAR/ACR score <10), inclusion of photosensitivity (defined as in the ACR-1997 criteria) or a combination of immunological and clinical features can still be used for SLE diagnosis. ACR, American College of Rheumatology; ANA,antinuclear antibody; EULAR, European League Against Rheumatism; SLE,systemic lupus erythematosus.

have increased risk of developing SLE compared with matched controls.[26 27]

Clinical course, activity patterns and adverse prognostic factors

In a large Canadian cohort, approximately 70% of patients with SLE followed a relapsing-remitting course, with the rest 30% divided equally between prolonged remission and persistently active disease (online supplemental figure S2).[28] Higher remission rates have been reported from Italy, with 37% of patients achieving prolonged remission; vasculitis, glomerulonephritis and haematological disease were associated with an unremitting disease.[29] Remission for at least two consecutive years is associated with halting of damage accrual.[30] cSLE, male patients, patients with low complement, positive anti-DNA or aPL antibodies, patients with high interferon (IFN) signature and patients with moderate to high activity indices are more likely to develop severe SLE.[1] Such patients should be ideally referred to centres where multidisciplinary care is offered, returning to their physician once a therapeutic plan is in place.

METROLOGY AND THE RATIONALE FOR MEASURING ACTIVITY AND DAMAGE INDICES

Due to the multiorgan involvement, there is a need for use of both global and organ-specific, validated disease activity indices to guide therapy and to serve as outcome for clinical trials. Three are the most widely used instruments: (1) SLE Disease Activity Index (SLEDAI); (2) British Isles Lupus Activity Group (BILAG) index and (3) Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI Physician Global Assessment (PGA).[31] Each index scores general signs and symptoms of disease activity in various organs, with the SLEDAI also scoring lupus serology, such as anti-dsDNA and serum complement levels. The SLEDAI is weighted, while BILAG provides a comprehensive set of definitions for mild, moderate and severe activity in multiple organs and according to the intention-to-treat concept (eg, BILAG A necessitates the use of high-dose glucocorticoids and/or immunosuppressives). PGA should complement objective activity indices, because the latter can miss certain items of disease activity or lack sensitivity to longitudinal changes. In our practice, we use the SLEDAI-2K version of SLEDAI (which allows persistent, rather than new-onset only, activity in alopecia, mucosal ulcers, rash and proteinuria to be scored),[32] combined with PGA, and the SELENA-SLEDAI definitions for flares (table 1). A newly proposed SLE Disease Activity Score (SLE-DAS; accessible at http://sle-das.eu/) with more items to include less common—yet severe—manifestations such as myositis, haemolytic anaemia, cardiopulmonary and gastrointestinal manifestations, has improved sensitivity to changes compared with the SLEDAI, while maintaining high specificity and easiness of use.[33]

In SLE, organ damage assessed by the SLICC/ACR Damage Index (SDI)[34] (table 1) is associated with adverse clinical outcomes and death. Although some SDI items are obscurely defined, it currently represents the single, validated and easy-to-use clinical tool to monitor complications or dysfunction across a wide range of organs due to active SLE, administered treatments (especially glucocorticoids) or associated comorbidities. With a

Table 1 Features, caveats and pitfalls of main indices used in SLE: the SLEDAI-2K, the SELENA-SLEDAI Flare Index and the SLICC/ACR Damage Index

Index	Features and clinical relevance	How to use, caveats and pitfalls
SLEDAI-2K	Features ► Scores the activity of 24 clinical presentations within a period of 28 days ► Organ involvement is weighted from 1 to 8 (range 0–105) Grading of severity ► SLEDAI=0 Remission ► SLEDAI=1–4 Low activity ► SLEDAI=5–10 Moderate activity ► SLEDAI >10 High activity Clinically important changes ► Increase >3 = Flare ► Decrease <3 = Improvement ► Change ±3 = Persistent activity	► Combine SLEDAI with a Physician Global Assessment (PGA) (graded from 0 to 3 on a 10 cm long straight line) ► Assess PGA before calculating the SLEDAI, to avoid bias in physician assessment ► Score items only if confidently *attributed to lupus* ► Pitfalls: pyuria due to UTI or asymptomatic bacteriuria; hair loss or leucopenia due to drug side effect; stroke due to atherosclerosis; other neuropsychiatric manifestations due to metabolic abnormalities, drug side effects or CNS infectionsScore items only if they are *reversible* ► Pitfalls: scarring alopecia; 'fixed' lupus rash with scar; 'fixed proteinuria'Time needed to complete: 5–10 min
SELENA-SLEDAI Flare index	Flares defined by: ► changes in SLEDAI score *and/or* individual manifestations *and/or* changes in treatment *and/or* need for hospitalisation *and/or* changes in PGA Mild/moderate flare ► Change in SELENA-SLEDAI instrument score of 3 points or more (but not to >12) ► Increase in prednisone, but not to >0.5 mg/kg/day ► Addition of NSAID, hydroxychloroquine for SLE activity ► ≥ 1.0 increase in PGA score, but not to >2.5 Severe flare ► Change in SELENA-SLEDAI instrument score to >12 points ► Increase in prednisone to >0.5 mg/kg/day ► New cyclophosphamide, azathioprine, methotrexate, MMF or biologics for SLE activity ► Hospitalisation for SLE ► Increase in PGA score to >2.5	► Patients classify for flare if ≥1 criterion for flare is present ► Treatment changes qualify for a flare, even in case of persistent activity rather than exacerbation ► A treatment change does not always correlate with physician assessment of disease activity ► A 'major flare' can result from *small* increases in disease activity from different domains ► No discrimination between mild vs moderate flares ► Both number and severity of flares have been associated with irreversible damage accrual (SDI increase) ► Time needed to complete: 10–20 min
SLICC/ACR DAMAGE INDEX (SDI)	Features ► Scores irreversible damage accrual in 12 organ systems ► Damage due to either disease or medication side-effects (eg, glucocorticoids or cyclophosphamide) Grading of damage ► SDI 0 No damage ► SDI≥1 Irreversible damage present ► SDI≥3 Severe damage present Clinical relevance ► Any increment in the SDI is prognostically significant, associated with further damage accrual and mortality	► Score damage occurring *only after* SLE onset ► Score items present for *at least 6 months* (beware for potentially reversible manifestations, eg, proteinuria, alopecia) ► Since damage items are irreversible, SDI *can only increase over time* (unlike eg, the Health Assessment Questionnaire in RA) ► Individual items get same score if present, irrespective of extent of damage and impact on patient's life Examples: Stroke with minimal neurologic sequelae vs severe neurologic deficit; pulmonary fibrosis limited vs extensive ► Time needed to complete: 10–20 min

ACR, American College of Rheumatology; CNS, central nervous system; MMF, mycophenolate mofetil; NSAID, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; SDI, SLICC/ACR Damage Index; SELENA, Safety of Estrogens in Lupus Erythematosus National Assessment; SLE, systemic lupus erythematosus ; SLEDAI, SLE Disease Activity Index; SLICC, Systemic Lupus International Collaborating Clinics; UTI, urinary tract infection.

maximum score of 46, any increment in the SDI is clinically and prognostically significant, reflecting the burden of the disease.

The use of validated activity and damage indices has been included in the EULAR guidelines for the management of SLE,[34] which recommend assessment of at least one activity index at each visit and of SDI once yearly. Free online calculators for both instruments can be found at https://qxmd.com/calculate/calculator_335/sledai-2k and https://qxmd.com/calculate/calculator_336/slicc-acr-damage-index.

OUTCOME MEASURES AND REMEDYING THE FAILURE OF MULTIPLE LUPUS TRIALS

During the past three decades, late-phase (IIb and III) clinical development programmes involving at least 40 novel agents have failed. While earlier trials from the Mayo Clinic and the United States National Institutes of Health used organ-specific outcome measures (for instance, in nephritis), subsequent trials have employed global outcome measures to capture general SLE activity and response.[33 35–37] In the belimumab trials, the SLE Responder Index (SRI) was developed as a composite outcome incorporating a modification of SELENA SLEDAI, BILAG, and a 0-3 Visual Analogue Scale of PGA to determine patient improvement. The BILAG-based Composite Lupus Assessment (BICLA), developed based on data from clinical trials of epratuzumab, requires patients to meet response criteria across three assessment tools, namely SLEDAI, BILAG and PGA. Not unexpectedly, differences in the structure of these two composite indices are reflected on differences in the response rates in recent SLE clinical trials.

A better appreciation of disease heterogeneity and its course; the lack of synchronisation of involvement and timing of response of different end-organs; the differential response of patients of various ancestries and geographic locations; the inclusion of patients with mild disease; the high dose of glucocorticoids and other background medications used; and finally, shortcomings of trial inclusion criteria (such as serology, biomarkers) and endpoints[38] have led the community to believe that improved metrics for treatment response are needed and

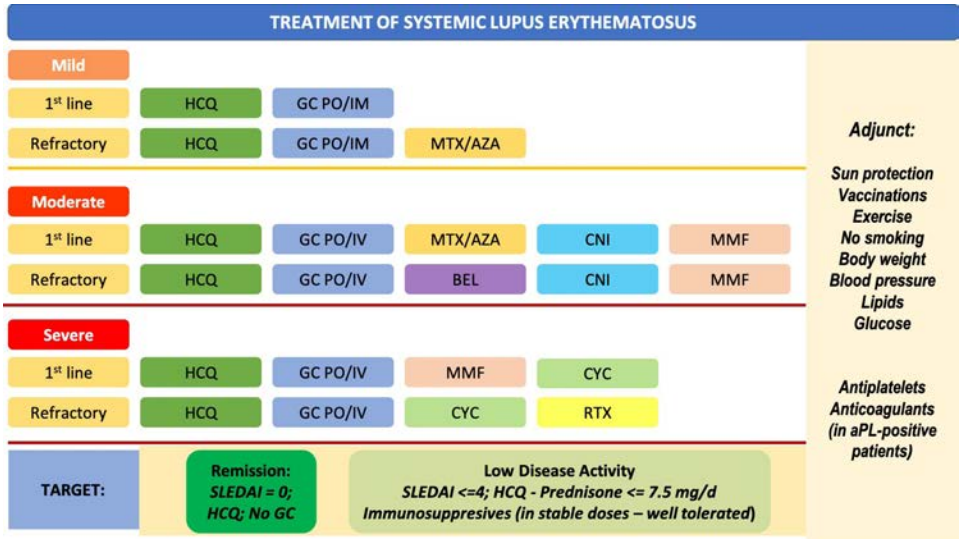

Figure 5 EULAR recommendations for the management of SLE drugs, treatment strategy, targets of therapy and adjunct therapy. Determination of severity in SLE is based on (a) the involvement of major organs or organ-threatening disease; (b) concomitant activity from multiple non-major organs; and (c) the need for the use of high doses of glucocorticoids and/or immunosuppressive therapy. aPL, antiphospholipid antibody; AZA, azathioprine; BEL, belimumab; CNI, calcineurin inhibitors; CYC, pulse cyclophosphamide; EULAR, European League Against Rheumatism; GC, glucocorticoids; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; RTX, rituximab; SLEDAI, SLE Disease Activity Index.

the use of organ-specific endpoints should be reconsidered. These caveats have forced investigators in more recent trials to pay more attention to these issues and modify designs and outcome measures accordingly. Molecular taxonomy and novel biomarkers for diagnosis, monitoring and treatment are available, but need to be further defined. For instance, while 75% of SLE patients have an IFN signature, only 50% of the patients respond to IFN-a inhibitors.[36]

An attempt has been made to define more rigorous response criteria and disease states, such as remission and lupus low-disease activity state (LLDAS)[33 34 39] (online supplemental box 1). LLDAS is a pragmatic and clinically relevant outcome, taking into consideration that (a) remission in SLE is desirable, but not always achievable, and (b) patients who spend more than 50% of their observed time in LLDAS have significantly reduced damage accrual.[40] Flare is an emerging trial outcome defined as any increase in disease activity leading to intensification of therapy.

MANAGEMENT OF SLE: WINNING THE WAR BY PREVAILING IN MULTIPLE BATTLES

General principles, targets of therapy and recommendations

Management recommendations have been published by EULAR in 2008 and were updated in 2019 based on emerging new data.[34 41] Of note, these recommendations represent guidance only, not strict instructions.[42 43] Treatment goals include long-term patient survival, prevention of organ damage and optimisation of health-related quality of life. Therapy should aim at remission or at least low disease activity and prevention of flares. All lupus patients should receive hydroxychloroquine, at a dose not exceeding 5 mg/kg real body weight (figure 5). During chronic maintenance treatment, glucocorticoids should be minimised to less than 7.5 mg/day (prednisone equivalent) and, when possible, withdrawn. Appropriate initiation of immunomodulatory agents (methotrexate, azathioprine, mycophenolate) can expedite the tapering/discontinuation of glucocorticoids. In persistently active or flaring disease, add-on belimumab should be considered; rituximab or cyclophosphamide (CY) may be considered in organ-threatening, refractory disease. In the recent update, specific recommendations were also provided for cutaneous, neuropsychiatric, haematological and renal disease. Patients with SLE should be assessed for their aPL antibody status, infectious and cardiovascular disease (CVD) risk profile, and preventative strategies should be adjusted accordingly.

Special considerations

Lupus nephritis

Lupus nephritis (LN) is a major cause for morbidity, increased medical expenses and mortality in SLE.[44] The life-long risk for severe nephritis is approximately 20%, although older reports may have overestimated these rates. Younger patients, especially males, those with active serology or with active moderate to severe non-renal lupus, are at higher risk for kidney involvement.[44] In reference to histological findings, strong predictors for progression into end-stage renal disease (ESRD) include the presence of extensive interstitial fibrosis/tubular atrophy and crescents[45] (online supplemental table S1). In a single-centre study from Milan reviewing cases from 1976 until 2016, risk factors for ESRD were male gender, hypertension, increased baseline creatinine, high histological activity and chronicity indices, and no use of maintenance immunosuppression.[46] ESRD-free survival rose from 80% to 90% at 20 years, attributed mainly to earlier diagnostic biopsies and prompt institution of immunosuppressive therapy (online supplemental box 2).[46]

In the updated 2019 EULAR/European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) recommendations for LN,[44] the target of therapy was set as a reduction in proteinuria by ≥25% with stable glomerular filtration rate (GFR; ±10% of baseline value) at first 3 months after treatment initiation; reduction by ≥50% in proteinuria at 6 months; and <0.5–0.7 g/24 hours proteinuria at 12–24 months (all with stable GFR).[47]

In active proliferative LN, initial (induction) treatment with low-dose intravenous CY (500 mg × 6 biweekly doses) or mycophenolate mofetil (MMF; 2–3 g/day, or mycophenolic acid at equivalent dose), both combined with glucocorticoids (pulses of intravenous methylprednisolone, then oral prednisone

0.3–0.5 mg/kg/day) is recommended. Combination of MMF with calcineurin inhibitors or high-dose CY are alternative regimens for patients with nephrotic-range proteinuria and adverse prognostic factors, respectively. Subsequent long-term maintenance treatment with MMF or azathioprine should follow. The need to minimise patient exposure to glucocorticoids has received more attention; in the updated EULAR/ERA-EDTA recommendations, following pulse IV methylprednisolone, recommended starting dose is 0.3–0.5 mg/day prednisone equivalent, which should be tapered to tapered to ≤7.5 mg/day by 3–6 months. Treatment in children follows the same principles as adult disease. EULAR recommendation-based treatment algorithms for proliferative and membranous LN can be found in online supplemental figures S3 and S4.

NPSLE: thrombotic or inflammatory and the problem of attribution

Neuropsychiatric events are diverse and most occur around the diagnosis of SLE.[48] Among them, seizures, cerebrovascular events and cognitive dysfunction are the most frequent. The risk of ischaemic stroke is more than twofold compared with the general population, with highest RRs within the first year after SLE diagnosis.[49] This presents an opportunity for rheumatologists to screen patients for risk factors and intervene early.[42 43] Importantly, approximately 60% of strokes occur in the presence of generalised lupus activity, which has implications for their management (see below). Although the majority of events resolve, they are associated with reduced health-related quality of life and excess mortality.[48]

Cognitive dysfunction is a significant problem in SLE and often occurs with limited or no structural brain abnormalities on conventional MRI. Using functional MRI in the assessment of cognitive function, Barraclough *et al*[50] showed that patients with SLE have poorer performance on a task of sustained attention and altered brain responses, particularly in default mode network regions and the caudate. The study highlighted that patients with SLE are likely to employ compensatory brain mechanisms to maintain cognitive performance and may score similarly to healthy controls in objective measures of cognition, but may fatigue quicker.

Attribution of neuropsychiatric manifestations to SLE (so-called 'primary NPSLE') is complex and requires a comprehensive, multidisciplinary approach to rule out mimics (infections, malignancy, comorbidities and others), by considering: (a) risk ('favouring') factors such as type and timing of manifestation, presence of generalised, non-neurological disease activity, abnormal neuroimaging and cerebrospinal fluid analysis, positive aPL antibodies; and (b) confounding factors favouring alternative diagnoses.[51] New MRI techniques may help to differentiate primary NPSLE from neuropsychiatric events unrelated to lupus. The former is characterised by hypoperfusion in cerebral white matter that appears normal on conventional MRI; we recently showed that co-registration of MRI with dynamic susceptibility contrast MR-measured blood flow in the brain semioval centre suggests primary NPSLE.[52]

Immunosuppressive therapy is recommended for NPSLE of presumed inflammatory origin, anticoagulation/antiplatelet therapy for manifestations presumed to be thrombotic or embolic, and their combination if both mechanisms are considered possible.[34] A large autopsy study that included both patients with NPSLE (70% of which had cerebrovascular accidents, mostly in the context of generalised lupus activity) showed that microthrombi were found uniquely in NPSLE and were associated with C4d and C5b-9 deposits, suggesting that complement deposition may be a key factor in the interaction between circulating autoantibodies and thromboischemic lesions observed in SLE.[53] These indirect data support the EULAR recommendation for a low threshold for immunosuppressive treatment in stroke, especially in the presence of generalised lupus activity and absence of aPL antibodies and atherosclerotic risk factors. An algorithm for the management of NPSLE can be found in online supplemental figure S5.

Haematological disease and emerging haematologic phenotypes

Autoimmune cytopenias are common in SLE. Haematological manifestations necessitating immunosuppressive treatment in patients with SLE include immune thrombocytopenia (see online supplemental figure S6 for its management) and haemolytic anaemia.[34] The presence of thrombocytopenia should prompt examination of the peripheral smear to exclude microangiopathic haemolytic anaemia (MAHA) and thrombotic microangiopathy (TMA). MAHA is non-immune haemolysis resulting from intravascular red blood cell fragmentation that produces schistocytes in the peripheral blood smear. TMA is a diverse syndrome that includes, among others, the classical thrombotic thrombocytopenic purpura (TTP) and is characterised by both MAHA and organ damage due to arteriolar and capillary thrombosis, with characteristic pathologic endothelial and blood vessels wall abnormalities that lead to microvascular thrombosis.[54] Not all MAHA is caused by a TMA syndrome, but virtually all TMAs cause MAHA and thrombocytopenia. In rare cases, MAHA may be a manifestation of catastrophic APS.

Most experts agree that TTP and SLE are distinct clinical syndromes and only rarely coexist. Lupus patients may have reduced levels of the metalloproteinase ADAMTS 13, a classical finding in TTP, which may be due to the presence of autoantibodies against the protein; this may pose difficulties in distinguishing SLE from TTP/TMA and overlapping features, such as severe CNS involvement, may make TTP indistinguishable from SLE exacerbation; in such cases, the use of plasmapheresis or rituximab may be considered. However, in most cases, MAHA in SLE responds to immunosuppressive therapy and does not require plasmapheresis.

Macrophage activation syndrome (MAS) is a rare but potentially fatal complication of SLE, presenting with febrile cytopenia mimicking lupus flares. MAS can coincide or follow the diagnosis of SLE and may relapse in up to 10% of patients.[55] High-dose glucocorticoids alone are used as first-line therapy; IV immunoglobulin, CY, rituximab and etoposide are also used, with etoposide and CY-based regimens having the best efficacy.[55]

Pulmonary hypertension and involvement of the heart

Pulmonary arterial hypertension is an infrequent but serious complication of SLE. Recent data suggest two distinct phenotypes, the vasculopathic with low lupus disease activity ('pure PAH') and the so-called 'vasculitic' with high lupus disease activity, which may be more responsive to immunosuppressive therapy.[56 57] Patients with lupus may also develop pulmonary hypertension via other mechanisms: chronic thromboembolic pulmonary hypertension due to non-resolving occlusion of the pulmonary vasculature or, less frequently, pulmonary hypertension secondary to interstitial lung disease causing hypoxaemia.

Although pericarditis is the most frequent heart manifestation, in SLE valvular disease and, less often, myocarditis may be detected. Both SLE and the presence of aPL increase the risk for valvular heart disease.[58 59] Myocarditis is rare yet increasingly recognised in SLE after the advent of heart MRI and use

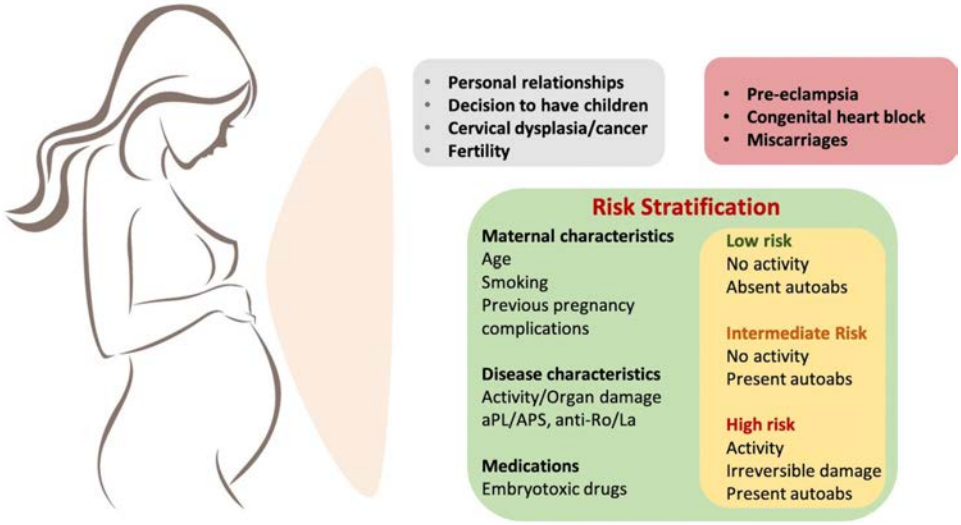

Figure 6 Women's health, fertility and pregnancy in women with SLE. SLE is impacting on personal relationships and family planning should be discussed as early as possible after diagnosis. Most women can have successful pregnancies and measures can be taken to reduce the risks of adverse maternal or foetal outcomes. A pregnancy risk stratification should take into account maternal characteristics, disease characteristics (activity, presence of autoantibodies) and received medications. Low disease activity before and during pregnancy and the use of hydroxychloroquine improve pregnancy outcomes. Underuse of low-dose aspirin use and high prevalence of pre-eclampsia risk factors among pregnant women have been recently reported, pointing to a major gap between practices and current recommendations for pregnant SLE women.SLE,systemic lupus erythematosus.

of high-sensitive troponin tests.[58 59] Antimalarial-induced cardiomyopathy is a rare, probably under-recognised complication of prolonged antimalarial treatment. It presents as a hypertrophic, restrictive cardiomyopathy with or without conduction abnormalities.[60]

Women's health, fertility and pregnancy in SLE

The risk of high-grade cervical dysplasia and cervical cancer is 1.5 times higher in women with SLE.[61] Accordingly, human papillomavirus immunisation should be recommended in all SLE women. SLE is impacting on personal relationships and the decision to have children.[62] Family planning should be discussed as early as possible after diagnosis. Hormonal contraception and menopause replacement therapy (if there is strong indication) can be used in patients with stable/inactive disease and low risk of thrombosis (figure 6).[63–65]

Most women can have successful pregnancies and measures can be taken to reduce the risks of adverse maternal or foetal outcomes. Risk factors for adverse pregnancy outcomes include active SLE; prior or current active LN; hypertension or proteinuria more than 1 g/day; presence of serological activity or aPL antibodies; previous vascular and pregnancy morbidity; and use of prednisone—a surrogate for active disease. In contrast, there are benefits from the use of hydroxychloroquine and antiplatelets/anticoagulants.[66] Increased Bb and sC5b-9—early in pregnancy—are strongly predictive of adverse pregnancy outcomes, supporting the role of activation of the alternative pathway complement.[67] Low rates of low-dose aspirin use and high prevalence of pre-eclampsia risk factors among pregnant women in a multinational SLE inception cohort have been recently reported, pointing to a major gap between practices and current recommendations for the care of pregnant SLE women.[68]

Congenital heart block (CHB) may develop in about 1% of fetuses of anti-Ro/SSA-positive women, including SLE. In a nation-wide healthcare registry, individuals with CHB had significantly increased risk for: (a) cardiovascular comorbidity manifested as cardiomyopathy and/or heart failure and cerebral infarction, (b) a systemic connective tissue disorder and (c) developing any of 15 common autoimmune conditions.[69]

Comorbidities

Infections

The net risk of infection in SLE is associated with both disease-related and treatment-related factors. Patients should receive vaccinations according to the EULAR recommendations.[70] Immunisation against seasonal influenza and pneumococcal infection (both PCV13 and PPSV23) is administered preferably during stable disease. Herpes zoster vaccination with the live vaccine (Zostavax) is available for the general population. In 90 patients with stable SLE not receiving intensive immunosuppression, Zostavax was well-tolerated and provoked an immune response.[71] Shingrix, a newer non-live vaccine, is safe and more effective to prevent shingles in the general population, although no studies have been performed in patients with lupus.

Patients with SLE may have a variable net state of immunosuppression, thus infection should be treated when in doubt. An elevated C reactive protein makes a bacterial infection more likely than a disease flare.[72] Prompt recognition and treatment of sepsis are essential; validated scores, such as the quick Sepsis-related acute Organ Failure (SOFA) score identifies patients at greater risk for a poor outcome in the emergency room or in hospitalised patients, by scoring three variables (altered mental status, tachypnoea and hypotension).

Cardiovascular disease

SLE is an independent risk factor for CVD, attributed both to traditional and to disease-related risk factors, such as persistent disease activity, LN, presence of aPL and use of glucocorticoids.[73] Use of statins should be considered on the basis of lipid levels and the presence of other traditional risk factors. Calculation of the 10-year CVD risk using, for instance, the Systematic Coronary Risk Evaluation (SCORE), is recommended,[74] although the actual risk is underestimated in patients with SLE. Maintaining blood pressure below 140/90 mm Hg may reduce

vascular events, therefore this should be considered the general target for patients with SLE.[75] However, patients with blood pressure >130/80 mm Hg and clinical CVD or a high estimated CVD risk (>10%) should be treated to a target< 130/80 mm Hg.[76 77] Moreover, patients with renal disease benefit from lower blood pressure targets, that is, below 120/80 mm Hg and the use of renin-angiotensin-aldosterone system inhibitors.[44] In a study from the Taiwan National Health Insurance Research Database, SLE was an independent predictor of in-hospital mortality following percutaneous coronary angioplasty (PCI) and was independently associated with overall mortality, repeat revascularisation and major adverse cardiovascular events. The study demonstrates the inherent risks associated with SLE in patients undergoing PCI and highlights the necessity to improve care and secondary prevention strategies for these high-risk patients.[78]

Malignancies

Rates of malignancies differ in patients with SLE compared with the general population.[79] There is an increased risk of haematological, lung, thyroid, liver, cervical and vulvovaginal, but a decreased risk of breast and prostate cancer. The risk for lymphoma is increased approximately threefold and has been linked to increased activity of multiple inflammatory cytokines, as well as possible viral causes.[80]

SURVIVAL AND MORTALITY AND THE IMPACT OF INCOME

In Western countries, the all-cause and cause-specific standardised mortality rates significantly decreased over time, likely reflecting the advances in the management of SLE and certain comorbidities. However, mortality rates are particularly high for patients aged less than 40 years. Results are not as good when looking at the global picture for SLE. After a period of major improvement, survival in SLE has plateaued since the mid-1990s in a review of 125 studies.[81] In high-income countries, 5-year survival exceeds 95% in both adults and children. In low-income/middle-income countries, 5-year and 10-year survival was lower among children than adults.[81]

RECENT CLINICAL TRIALS: PAVING THE WAY FOR THE FUTURE

New disease-modifying conventional and biologic agents used alone, in combination or sequentially, have improved rates of achieving treatment goals, including minimisation of glucocorticoid use. More specifically, studies have shown that MMF or enteric-coated mycophenolate sodium is equally effective to CY and superior to azathioprine in studies of patients with general lupus or LN.[34 82] Calcineurin inhibitors added to standard-of-care induction therapy for LN (so called 'multitarget' therapy) may increase complete renal remission rates and maintain remission. The first regimen tested included tacrolimus in combination with MMF and glucocorticoids, as both induction and maintenance therapy.[83 84] The AURA-LN phase 2 study tested the novel calcineurin inhibitor voclosporin for efficacy and safety in active LN. Its addition to MMF and glucocorticoids for induction therapy of active LN resulted in a superior renal response, but higher rates of adverse events including death were observed.[85] A subsequent phase 3 study recently confirmed superior efficacy without safety concerns (still in abstract form).[86]

In reference to biologics, new studies have confirmed earlier data on the efficacy of belimumab. In patients with SLE from

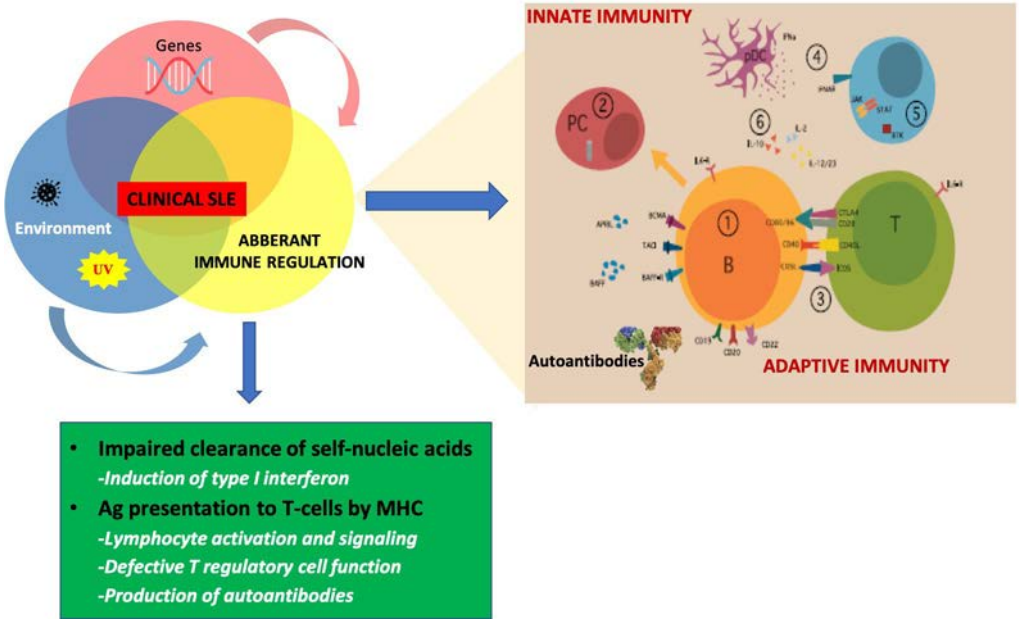

Figure 7 Pathogenesis and novel therapies in SLE. In SLE, genetic and environmental interactions culminate into aberrant regulation of both innate and adaptive immune responses, with excessive production of IFN-α and autoantibodies. Aberrant lymphocyte activation due either to altered activation threshold and/or defective T-regulatory cell function are key pathogenetic features of SLE. The cells and molecules of the immune system that have been targeted or are in the process of testing for clinical efficacy in SLE are shown in the figure: (1) B-cell (1; 2) plasma cell; (3) B–T-cell co-stimulation; (4) IFNs or their receptors; (5) intracellular kinases; (6) cytokines or their receptors. Combination therapy targeting both innate and adaptive immune responses may be more effective in assuring major, sustained clinical responses in SLE. Figure on the right modified from Klavdianou K, Lazarini A and Fanouriakis A. *BioDrugs* 2020;34:133–147. APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; ICOS, inducible T-cell costimulatory; ICOSL, ICOS ligand; IFN, interferon; IL, interleukin; JAK, Janus kinase; PC, plasma cell; pDC, plasmacytoid dendritic cell; SLE, systemiclupus erythematosus; STAT, signal transducer and activator of transcription; TACI, transmembrane activator and CAML interactor.

North East Asia, belimumab significantly improved disease activity and reduced severe flares while reducing prednisone use. A recent study compared organ damage progression in patients who received belimumab in the BLISS long-term extension study with propensity score-matched patients treated with standard of care from the Toronto lupus cohort. Patients receiving belimumab were 61% less likely to progress to a higher SDI score over any given year compared with patients treated with SoC (HR 0.39).[87] In adults with active LN, the Efficacy and Safety of Belimumab in Patients with Active LN (BLISS-LN) study, involving 448 patients, met its primary endpoint, demonstrating that a statistically significant greater number of patients achieved primary efficacy renal response over 2 years when treated with belimumab plus standard therapy compared with placebo (43% vs 32%, OR (95% CI) 1.55 (1.04 to 2.32).[88]

Anifrolumab, a human monoclonal antibody to type I IFN receptor subunit 1, did not have a significant effect on the SRI (primary endpoint) in the Treatment of Uncontrolled Lupus via the Interferon Pathway (TULIP)-1 phase 3 trial. By contrast, the TULIP-2 phase 3 trial used as its primary endpoint the British Isles Lupus Assessment Group (BILAG)–based Composite Lupus Assessment (BICLA), a secondary endpoint from the TULIP-1 trial. A BICLA response requires (1) reduction in any moderate-to-severe baseline disease activity and no worsening in any of nine organ systems in the BILAG index, (2) no worsening on the SLEDAI, (3) no increase of ≥0.3 points in PGA, (4) no discontinuation of the trial intervention and (5) no use of medications restricted by the protocol. The discrepancy of the results in TULIP-1 and TULIP-2 may be due to differences in the pathophysiology of various organs involved in SLE, differences between the SRI and the BICLA (for instance, SRI counts only complete responses, while BICLA also counts partial responses) and differences in the respective weights of the various organs involved and the serology (BICLA does not take serology into account).[37]

OPEN QUESTIONS, UNMET NEEDS EMERGING AND FUTURE THERAPIES

SLE continues to be a challenging and disabling disease, but there is now a better understanding of its causes, earlier recognition of its symptoms and signs, and more effective and less toxic drugs. Following the approval of belimumab,[89 90] advances in lupus research have led to new clinical trials for investigational drugs, each with a unique mechanism of action (figure 7). These include, but are not limited to, antibodies targeting B-cells or T-cells or their interaction, dendritic cells, IFN and other cytokines, and finally, low-dose IL-2 to boost regulatory T-cell function. Recent successes, such as the baricitinib trial[91] and the positive results from the TULIP-2 study of anifrolumab,[36] as well as low-dose IL-2,[92] provide room for cautious optimism. NPSLE is an emerging frontier for lupus research and care, encompassing a wide spectrum of clinical manifestations and complex pathophysiologic mechanisms that remain poorly understood.[93] Treatment of other aspects of SLE, such as skin, neuropsychiatric and haematologic disease, or of symptoms such as fatigue and headache, continues to be problematic. Whether there is a molecular, biological or imaging signature for these endotypes is not clear. To this end, development of organ-specific outcome measures (such as the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), for cutaneous lupus) may facilitate drug development for different subtypes of the disease.

Twitter Dimitrios T Boumpas @none

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ORCID iDs
Antonis Fanouriakis http://orcid.org/0000-0003-2696-031X
George Bertsias http://orcid.org/0000-0001-5299-1406
Dimitrios T Boumpas http://orcid.org/0000-0002-9812-4671

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Trajectories of COVID-19 information in the Annals of the Rheumatic Diseases: the first months of the pandemic

Kim Lauper [1,2], Johannes W J Bijlsma [3], Gerd R Burmester [4]

Handling editor Josef S Smolen

[1]Division of Rheumatology, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland
[2]Centre for Epidemiology Versus Arthritis, Centre for Musculoskeletal Research, University of Manchester, Manchester, UK
[3]Department of Rheumatology and Clinical Immunology, UMC Utrecht, Utrecht, Netherlands
[4]Department of Rheumatology and Clinical Immunology, Charité – Universitätsmedizin Berlin, Freie Universitität und Humboldt-University Berlin, Berlin, Germany

Correspondence to
Dr Kim Lauper, Division of Rheumatology, Geneva University Hospitals, 1205 Genève, Switzerland; Kim.Lauper@hcuge.ch

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INTRODUCTION

The COVID-19 pandemic shattered our world, whether at home or in our professional lives. Many of our colleagues or us were in the frontlines. Family and friends turned ill. Meanwhile, researchers all around the world rushed to understand this new disease, evaluate its course and find a cure. As rheumatologists and researchers in rheumatology, we have a deep understanding of the immune system, whether in reaction to an infection or during the course of a rheumatologic disease, and its interplay with the wide range of immunomodulatory treatments available. We also need to understand how this disease impacts our patients. Therefore, since the beginning of the pandemic, the rheumatology community is at the forefront of COVID-19 related research. From the first letter on COVID-19 in March 2020[1] to the end of September, the Annals of the Rheumatic Diseases (ARD) have published more than 200 letters, correspondences, originals studies and other articles (figure 1). The first publication on COVID-19 in ARD by Figueroa-Parra *et al* 'Are my patients with rheumatic diseases at higher risk of COVID-19?' already illustrated the most burning questions of the rheumatology community: the potential risks of infection or severe outcome associated with the rheumatic diseases themselves or their therapy and the efficacy of antimalarial drugs in treating COVID-19.[1] Other topics that were widely discussed were the drug shortage of hydroxychloroquine, the use of telemedicine and the effect of the pandemic on patients. In this brief review of ARD publications on COVID-19, we will explore how perceptions and information changed and how interests shifted from one topic to another during the last months.

TYPE OF PUBLICATIONS IN ARD

Most of the publications on COVID-19 from March 2020 to September 2020 on COVID-19 were letters, correspondences and correspondence responses (figure 1). Around half presented original data, mainly in the form of a short correspondence (72%), from which the quality is difficult to assess. The great majority of studies (76%) were only descriptive, and all were observational. Almost half were case reports or case series (47%). The first complete original studies published in extended/concise reports were published end of May 2020,[2–4] and comprised a progressively higher proportion of all the COVID-19 publications the months thereafter, while letters and correspondences decreased (figure 1).

The first recommendations were published in April, with a letter describing the 'Preliminary recommendations of the German Society of Rheumatology (DGRh eV) for the management of patients with inflammatory rheumatic diseases during the SARS-CoV-2/COVID-19 pandemic' and a recommendation article for the management of systemic sclerosis: 'Systemic sclerosis and the COVID-19 pandemic: World Scleroderma Foundation preliminary advice for patient management'.[5 6] The "European League AgainstRheumatism (EULAR) provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2' appeared in June.[7] All of these recommendations are provisional, as they were based on the knowledge at the time, and as we will see, this may change swiftly. However, most of the points that were discussed, are still up to date. Update of the EULAR recommendations is planned.

RHEUMATOLOGICAL DISEASES AND THEIR TREATMENTS

The fall from grace of hydroxychloroquine

With their potent in vitro action on coronaviruses and promising results on case series and small trials, antimalarial drugs were the main focus during the first months of the pandemic and promptly discussed as a potential preventive therapy or treatment[8 9] (figure 2A). As we will see later, this will also have an important impact on drug availability for patients with rheumatological diseases. In the first weeks, the positive perception of the therapy is such, that in a study of rheumatology practitioners from India, 67% were more inclined to favour the prescription of antimalarial in their patients.[10] However, others advised to be cautious as rigorous studies were lacking.[11–13] Indeed, from mid-April, the first case series appeared, demonstrating that patients treated for their rheumatological disease with hydroxychloroquine could be infected and present severe outcomes.[14 15] Simultaneously, arrhythmias were described in patients with COVID-19 that could possibly worsen with antimalarial therapy.[16 17] However, some authors argued that the absence of effect of antimalarial therapy could be confounded by the high comorbidity burden and the frequent association with glucocorticoids in infected patients with rheumatological diseases.[15] Yet, further studies in larger cohorts failed to find any differences in the evolution of patients treated with antimalarials or not.[4 18] In June, reflecting the state of knowledge also outside of the publications in ARD, the

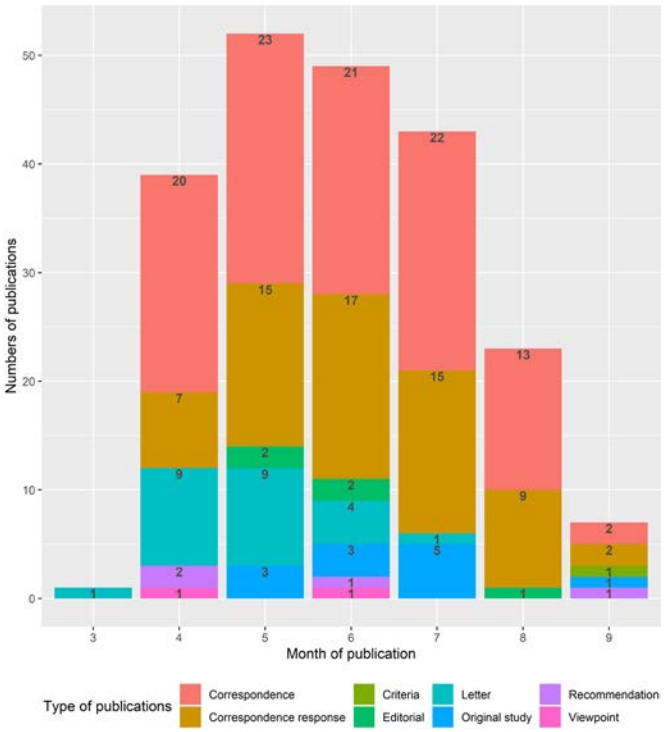

Figure 1 Numbers of publications about COVID-19 from March to September 2020 in the Annals of the Rheumatic Diseases by month and type.

perspective on antimalarials was shifting, with less and less publications postulating an effect of antimalarial therapy.[19–21] Indeed, the disinterest in antimalarial therapy as an option in COVID-19 prevention and treatment is mirrored in the decrease in publications on the subject (figure 2A).

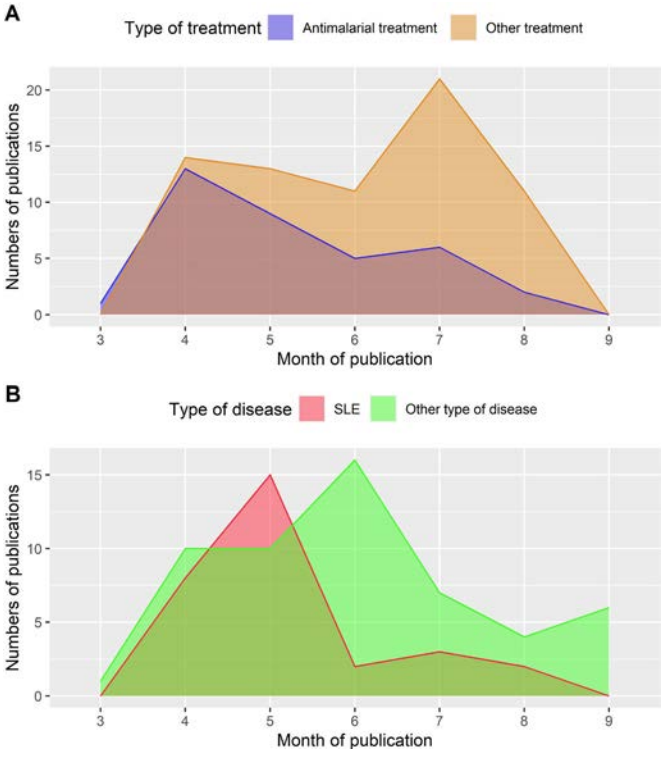

Figure 2 Numbers of publications about COVID-19 in the Annals of the Rheumatic Diseases from March to September 2020 by month and (A) type of treatment and (B) type of disease. SLE, systemic lupus erythematosus.

DMARDs: friend or foe?

Except for antimalarials, which were almost only discussed as a potential treatment, all other treatments were discussed as risk factors and as a potential therapy. Throughout the months, publications were intertwined between manuscripts discussing antirheumatic treatment in patients with rheumatological diseases and patients with non-rheumatological diseases.

None of the other classes of disease-modifying antirheumatic drugs (DMARDs) alone was as much debated as antimalarial therapy. Yet, other DMARDs were discussed from the start (figure 2A). Several small studies did not point to an increased rate of COVID-19 or more severe outcomes with DMARDs, including biological DMARDs (bDMARDs).[22–26] A study on 600 patients with COVID-19 from the COVID-19 Global Rheumatology Alliance failed to find an increase in the risk of hospitalisation with bDMARDs after adjusting for several confounding factors such as disease activity and comorbidities.[4] However, describing two fatal cases of COVID-19 under rituximab, Schulze-Koops *et al* advised against a too reassuring and potentially hazardous narrative.[27] Some authors postulated that low rates of COVID-19 in patients with rheumatological musculoskeletal diseases may rather be associated with protective measures such as social distancing and personal protective equipment, which were adopted by the majority.[28]

When looking at DMARDs as a treatment, anti-interleukin-6 (anti-IL-6) therapy was one of the first treatment option discussed against the 'cytokine storm' of a severe course of COVID-19, beginning with case reports,[29] small studies,[30 31] and finally larger observational cohorts with historical or matched comparators, which were among the first studies in the literature comparing IL-6 therapy to standard of care,[31 32] with promising results. On the other hand, inhibition of IL-6 seemed also to increase the risk of COVID-19 infection and infections in general.[33 34] Glucocorticoids were alternatively associated with worse[4 35 36] or improved outcomes,[37 38] without a clear trend emerging as it appeared to be a risk factor of infection, but clearly beneficial when ventilation was needed. Glucocorticoids are now part of treatment algorithms used in most hospitals. Although one of the most frequent classes of bDMARDs prescribed, only a few articles specifically addressed the potential benefits of tumour necrosis factor-inhibitor therapy.[39 40] Case series and studies describing a potential advantage of IL-1 inhibition and colchicine were also reported.[41–44]

In their editorial in August 2020 'To immunosuppress: whom, when and how? That is the question with COVID-19', Winthrop and Mariette expertly summarised the current knowledge on these different therapies. They postulated that some treatments may be deleterious when given too soon and lose their efficacy if given too late, with the current ongoing challenge of finding the potential 'sweet spot'.[45] Hopefully, the publication of new criteria defining the 'cytokine storm' will help to identify patients that will need specific treatment for this condition.[46]

Effect of the rheumatological diseases on COVID-19 infection and its outcome

Following the trend of antimalarial therapy and COVID-19, systemic lupus erythematosus (SLE) was also one of the 'hot topics' of the first months (figure 2B). A letter published beginning of April hypothesised that the absence of cases of infection described in patients with SLE despite thousands of cases

of COVID-19 could be linked to their treatment with hydroxychloroquine.[47] However, other researchers immediately urged to be cautious with such claims.[48 49] Indeed, 1 week thereafter, case series presenting the clinical course of COVID-19 in 17 patients with SLE and long-term hydroxychloroquine treatment were described,[14] rapidly followed by a description of larger cohorts of patients with SLE and antimalarial treatment.[15]

Although no single rheumatological disease was as much discussed as SLE (figure 2B), the potential increased risk of COVID-19 infection and severe outcomes with other rheumatological diseases was investigated from the start. The first studies did not report an increase in complications or admission to the intensive care unit.[50 51] However, later studies, although confirming partially these results, found a higher risk of severe pulmonary disease.[3] Finally, it appeared that maybe distinct types of rheumatological disease may confer different risks, with systemic auto-immune diseases associated with an increased risk of hospitalisation compared with inflammatory arthritides.[52 53]

The only consensus that appears to stay throughout the months, when discussing the risk of the diseases themselves or their treatment, is that uncontrolled disease activity should be prevented, as this may increase the risk of infections, and that patients should not stop therapy pre-emptively.[54 55]

Drug shortage

Due to the enthusiasm of antimalarial therapies in COVID-19, the possibility of drug shortage rapidly became a cause of concern.[11] All around the globe, physicians and patients were confronted with difficulties in accessing antimalarial drugs with as much as 70% of physicians and patients directly concerned.[56–58] Rheumatologists agreed at this time that, although antimalarial therapy might appear as an option for COVID-19, enough supply for clear and proved indications such as rheumatological diseases should be assured and prioritised.[59] Fortunately, in most countries, measures were rapidly taken at the system level to allocate drug treatment to patients with rheumatological diseases, while waiting for a clear indication of efficacy in COVID-19.[60]

TELEMEDICINE

In line with the 'stay at home' advice and because of a lockdown in some countries as well as a focus of the healthcare system on COVID-19 cases, telemedicine rapidly became an invaluable tool and was swiftly implemented in most clinics.[61] Telemedicine seemed to be readily accepted by patients, although older patients or patients with higher disease activity appeared to be less satisfied.[62 63] Understandably, patients were not in favour of a telemedicine follow-up if they had to come to the clinics for laboratory testing.[63] Rheumatologists also appeared to support telemedicine but expressed that it may not be appropriate for follow-up of active disease in the treat to target era and patients at risk of organ damage. Careful selection of patients who could be followed through telemedicine was thus considered essential.[64–66] In addition, as non-specific systemic symptoms are often a hallmark of rheumatic diseases, it was feared that they might be falsely attributed to COVID-19 through telephone triage, impacting speed of diagnosis. Indeed, an increase in the incidence of blindness in giant cell arteritis because of delayed diagnosis was reported.[67] Interestingly, in developing countries, difficulties in implementing telemedicine, when internet access is not always readily available, were as much discussed as the benefits it could provide, when there were no local rheumatologists available.[68]

THE PATIENT'S PERSPECTIVE

A few studies evaluated the impact of COVID-19 on patients with rheumatological diseases, mainly discussing adherence and drug shortage. Although fear of contracting the infection was high, most of the patients perceived the benefit of their medications as superior and only few patients reduced their treatment because of the pandemic, sadly primarily because of drug shortage.[26 69–71] Fortunately, this did not seem to have an important impact on disease activity.[72] Patients appeared also to follow preventive measures with as much as 90% of them practising social isolation and/or using personal protective equipment.[28] Regrettably, the social isolation imposed by the pandemic also took a toll on patients' quality of life with a decrease in both mental and physical components.[73]

CONCLUSION

The publications on COVID-19 in ARD during these last months are representative of the shifting landscape about COVID-19 knowledge, starting with small case reports followed by wider studies giving a much broader and accurate perspective, and the rapid development of provisional recommendations to help manage rheumatological diseases during the pandemic.[7] The scientific methods involve the formulation of hypotheses, based on current knowledge and observation, inductive and deductive reasoning, testing and refining of the hypotheses. Assumptions that appeared promising at first, can be smashed in the process or confirmed. The articles published in ARD are no exceptions, which spreads a reassuring light on the commitment of the rheumatology community to improve scientific knowledge. The profound knowledge that the rheumatological community, including basic researchers, has about the immune system bring rheumatologists at the forefront of the scientific progress in this field. COVID-19 also opened new perspectives in the treatment of patients with telemedicine, their fears, their trust in their therapy and the sobering effect of the endorsement of unfounded therapies on drug supply.

While we face uncertain times ahead, the swift ability to adapt to change of the wide rheumatology community, including patients, researchers and healthcare practitioners, whether in terms of clinical knowledge or clinical practice, is a steady foundation on which we can hope to build a brighter future.

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ORCID iDs
Kim Lauper http://orcid.org/0000-0002-4315-9009
Johannes W J Bijlsma http://orcid.org/0000-0002-0128-8451
Gerd R Burmester http://orcid.org/0000-0001-7518-1131

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EULAR definition of difficult-to-treat rheumatoid arthritis

György Nagy ,[1,2] Nadia MT Roodenrijs ,[3] Paco MJ Welsing,[3] Melinda Kedves ,[4] Attila Hamar,[5] Marlies C van der Goes,[3,6] Alison Kent,[7] Margot Bakkers,[8] Etienne Blaas,[3] Ladislav Senolt,[9] Zoltan Szekanecz ,[5] Ernest Choy,[10] Maxime Dougados,[11] Johannes WG Jacobs ,[3] Rinie Geenen,[12] Hans WJ Bijlsma,[3] Angela Zink,[13] Daniel Aletaha ,[14] Leonard Schoneveld,[15] Piet van Riel,[16] Loriane Gutermann,[17] Yeliz Prior,[18] Elena Nikiphorou ,[19] Gianfranco Ferraccioli ,[20] Georg Schett ,[21] Kimme L Hyrich,[22,23] Ulf Mueller-Ladner,[24] Maya H Buch ,[22,23,25] Iain B McInnes,[26] Désirée van der Heijde ,[27] Jacob M van Laar[3]

Handling editor David S Pisetsky

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For numbered affiliations see end of article.

Correspondence to
Professor György Nagy, Department of Rheumatology, Semmelweis University, Budapest, Árpád fejedelem útja 7., 1023, Hungary; nagy.gyorgy2@med.semmelweis-univ.hu

DvdH and JMvL contributed equally.

DvdH and JMvL are joint senior authors.

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ABSTRACT

Background Despite treatment according to the current management recommendations, a significant proportion of patients with rheumatoid arthritis (RA) remain symptomatic. These patients can be considered to have 'difficult-to-treat RA'. However, uniform terminology and an appropriate definition are lacking.

Objective The Task Force in charge of the "Development of EULAR recommendations for the comprehensive management of difficult-to-treat rheumatoid arthritis" aims to create recommendations for this underserved patient group. Herein, we present the definition of difficult-to-treat RA, as the first step.

Methods The Steering Committee drafted a definition with suggested terminology based on an international survey among rheumatologists. This was discussed and amended by the Task Force, including rheumatologists, nurses, health professionals and patients, at a face-to-face meeting until sufficient agreement was reached (assessed through voting).

Results The following three criteria were agreed by all Task Force members as mandatory elements of the definition of difficult-to-treat RA: (1) Treatment according to European League Against Rheumatism (EULAR) recommendation and failure of ≥2 biological disease-modifying antirheumatic drugs (DMARDs)/targeted synthetic DMARDs (with different mechanisms of action) after failing conventional synthetic DMARD therapy (unless contraindicated); (2) presence of at least one of the following: at least moderate disease activity; signs and/or symptoms suggestive of active disease; inability to taper glucocorticoid treatment; rapid radiographic progression; RA symptoms that are causing a reduction in quality of life; and (3) the management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient.

Conclusions The proposed EULAR definition for difficult-to-treat RA can be used in clinical practice, clinical trials and can form a basis for future research.

INTRODUCTION

European League Against Rheumatism (EULAR) recommendations provide valuable guidance to direct the management of rheumatoid arthritis (RA). The treat-to-target (T2T) strategy advises an agreed disease activity target, remission or at least low disease activity, that can in turn inform responsive treatment escalation.[1–3] However, a number of patients remain symptomatic despite recommended treatment changes reflecting the complex interplay of disease and wider patient and clinical factors that leads to the increasingly recognised term of 'difficult-to-treat RA'.[4–7]

A recent international survey of rheumatologists highlighted the perceived management problems and features in this patient category; the results of which confirmed the unmet need of this subpopulation of RA patients.[8] The survey indicated that in addition to new drugs, new management approaches are also needed for the optimal treatment of these patients. Consequently, a EULAR Task Force was established to derive comprehensive recommendations addressing unmet needs in the management of difficult-to-treat (D2T) RA. Uniform terminology and a clear definition for this patient group are lacking. In the current literature, different terms are used to describe this subpopulation of RA patients, for example, severe, refractory, resistant to multiple drugs or treatments, established and difficult-to-treat.[4–7] As an initial step in the development of the management recommendations for D2T RA, terminology and a definition of this complicated RA patient group was established by the Task Force, guided by the results of the survey.[8]

METHODS

Steering committee and task force

The Steering Committee of the Task Force included a convenor (GN), co-convenor (JMvL), two methodologists (PMJW and DvdH) a rheumatology postdoctoral fellow (MJHdH) and three fellows (NMTR, MK and AH). The Task Force comprises 32 individuals (including the Steering Committee members) of which 25 members were present at the first Task Force meeting, which took place in August 2018. Among the Task Force members, there were 26 rheumatologists (including two EMerging EUlar

Network (EMEUNET) representatives), two patient partners, one health professional, one psychologist, one pharmacist and one occupational therapist. All rheumatologists are experienced in the treatment of RA, the majority with significant experience in clinical trials and a proportion in outcomes research. Numerous Task Force members have a leading role in organising and evaluating patient registries. All Task Force members declared their potential conflicts of interest before the start of the project.

Survey

An online survey was conducted among rheumatologists to identify characteristics of D2T RA; the survey was distributed by email via the authors' networks and by EMEUNET. The survey consisted of nine questions, including two general questions 'Where do you work? How many RA patients do you treat?', and four multiple-choice and three open questions regarding the definition of D2T RA. Four hundred and ten respondents from 33 countries completed the survey between July 2017 and March 2018, 96% of the respondents were European.[8]

Development of terminology and definition for D2T RA

The Steering Committee created the first draft of the definition based on the results of the survey and on a scoping literature search that was performed to explore different definitions that currently have been used (by NMTR, MJHdH and PMJW, see, online supplemental material 1). The results of the survey, the proposed terminology and the draft definition were presented to the Task Force at the first Task Force meeting. The definition was divided into three parts: treatment failure history, characterisation of active/symptomatic disease and clinical perception.

Agreement process

After the presentation of the draft terminology and definition, the general concepts were discussed and amended. Thereafter, the detailed wording was discussed and amended until consensus was reached. A voting process was conducted for each item of the terminology and definition. In case no consensus was reached among the present Task Force members, the preferred version was selected by voting. Twenty-one Task Force members were present during this discussion and voting process. After the meeting, two versions of the definition were distributed among all Task Force members to select the final version.

RESULTS

Terminology

At the first Task Force meeting, based on a scoping literature search and the suggestions of the Task Force members a variety of potential terms to describe this patient population were presented, including severe, refractory, multidrug/treatment resistant and complex RA. None of these terms was deemed to cover the wide range of possible clinical scenarios which may be relevant for this patient population. Since 'difficult-to-treat' is a widely accepted term in several fields including pulmonology, psychiatry and cardiology[9–11] this terminology was finally proposed by the Steering Committee and unanimously endorsed by the Task Force (21/21 agreed by voting).

Definition

Thereafter, we sought to create a definition of D2T RA based on the results of the previously mentioned international survey[8] and expert opinions. The Task Force agreed that both articular and extra-articular components should be considered and agreed to include the following criteria in the definition: (1) treatment failure history; (2) characterisation of active/symptomatic disease; and (3) clinical perception. All three criteria need to be present to confirm the state of D2T RA.

Criterion #1: treatment failure history

In the survey, 48% of the respondents selected '≥2 conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) AND ≥2 biological (b)DMARDs or targeted synthetic (ts) DMARDs with different mode of action' for the number and type of antirheumatic drugs that should have failed before a patient can be considered to have D2T RA. The Steering Committee initially proposed to include treatment duration in the definition 'Treatment according to the current standard of care/EULAR recommendations for ≥1 year'. This was chosen so that D2T RA patients are in phase III of the current RA management recommendations, in which no recommendation is given other than to switch to another b/tsDMARD.[1] However, inclusion of a certain time period in the definition was not supported by all Task Force members (primarily in order to provide flexibility) and the Task Force voted against referral to a treatment duration period for the definition of D2T RA (19/21 agreed, 2 abstained).

All Task Force members agreed to include the number of DMARDs previously failed in the definition and to create the definition consistent with the current EULAR RA management recommendations. 'Failure of at least two b/tsDMARDs with different mode of action' was selected by the majority of the respondents of the survey.[8] Although according to the current EULAR recommendations[1] no prioritisation for switching mechanism of action versus cycling is stated, it was decided that before being classified as D2T RA, a patient should at least have failed two b/tsDMARDs with different mechanisms of action. Consequently, it was decided to select this cut-off by the Task Force. With this cut-off, patients had to have completed phase III of the recommendations at least once (ie, they may also have been treated with multiple bDMARDs of a single class (eg, several tumour necrosis factor inhibitors) and also have failed another b/tsDMARD). Finally, all members agreed to select the following proposal: 'Treatment according to EULAR recommendation and failure of ≥2 b/tsDMARDs with different mechanisms of action after failing csDMARD therapy (unless contraindicated)' (21/21 agreed). This also indicates that if csDMARD treatment is contraindicated, failure of ≥2 b/tsDMARDs with different mechanisms of action is sufficient.

Socioeconomic factors may limit the access to expensive DMARDS (eg, in low income countries), therefore (with the agreement of all Task Force members) we have added to the first criterion: 'unless restricted by access to treatment due to socioeconomic factors'.

Criterion #2: characterisation of active/symptomatic disease

Fifty per cent of the respondents of the international survey selected 'disease activity score assessing 28 joints using erythrocyte sedimentation rate (DAS28-ESR)>3.2 OR presence of signs suggestive of active inflammatory disease activity with a DAS28-ESR≤3.2' as a characteristic of D2T RA. Additionally, 95% of the respondents of the international survey suggested to include the inability to taper glucocorticoids (GCs) in the criteria of D2T.[8] Therefore, the Steering Committee proposed the following characterisation of active/symptomatic disease: 'Presence of active disease defined as ≥1 of: (1) DAS28-ESR>3.2; (2) Presence of signs suggestive of active RA; and/or (3) Inability to taper oral glucocorticoids (below 7.5 mg/day prednisone or

equivalent)'. At the Task Force meeting, it was decided to include not only DAS28, which was the only composite disease activity measure offered in the survey, but to rather use a more generic definition: 'at least moderate disease activity (according to validated composite measures including joint counts, for example, DAS28-ESR>3.2 or clinical disease activity index (CDAI)>10)' (21/21 agreed). In addition to clinical signs and symptoms, it was agreed that this clarification should also include imaging and biochemical markers suggestive of active disease.

Furthermore, all Task Force members agreed that not only patients with joint-related problems should qualify to be defined as being D2T. Extra-articular manifestations, such as vasculitis, pericarditis, scleritis or glomerulonephritis may complicate the management of RA, and were therefore decided to be included in the definition. This resulted in the following wording: 'Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other)' (21/21 agreed).

In the survey, 43% of the respondents selected to include 'unable to taper glucocorticoids below 5 mg prednisone or equivalent daily' and 46% selected 'unable to taper glucocorticoids below 10 mg prednisone or equivalent daily' (in addition, another 6% chose to include inability to taper GCs, although with a different, unspecified dose).[8] At the Task Force meeting, it was decided to include the following definition as a compromise: 'Inability to taper oral glucocorticoids (below 7.5 mg/day prednisone or equivalent)'. The Task Force voted to keep this item in the definition (19/21 agreed).

During the Task Force meeting, additional possible signs of active disease were explicitly suggested for inclusion in the definition. First, the Task Force agreed to include rapid radiographic progression in the definition as a possible feature of D2T RA, as this might be occasionally observed even in case of clinically inactive disease. The following was proposed: 'Rapid radiographic progression (with or without signs of active disease)' (21/21 agreed). Second, non-inflammatory disease was considered, since these complaints, for example, concomitant fibromyalgia, might mimic inflammatory activity. Non-inflammatory disease may lead to several aforementioned characteristics of active/symptomatic disease. Furthermore, non-inflammatory disease might also lead to other clinically important complaints. Therefore, to ensure that patients with non-inflammatory complaints could be classified as having difficult-to-treat RA, it was suggested and unanimously agreed to add 'Well-controlled disease according to above standards, but still having RA symptoms that are causing a reduction in quality of life' (21/21 agreed).

The Task Force discussed whether to add fatigue to the definition, as this is one of the most common problems.[12 13] Since fatigue can diminish quality of life, it was suggested to be already included in the definition. In accordance with the survey (58% of respondents suggested not to include fatigue),[8] all Task Force members agreed to leave out the explicit mentioning of fatigue from the definition of D2T RA (21/21 agreed).

Criterion #3: clinical perception

As a final criterion, the Steering Committee suggested to include 'The disease is perceived as problematic by the rheumatologist and/or the patient'. This suggests that only clinical scenarios which are judged as problematic (eg, apparently ineffective treatment) are referred to as D2T RA. Since the definition is only applicable to patients in which a management problem is present, it was agreed to adapt the definition accordingly: 'The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient'. There were some concerns that this criterion might be too subjective, especially for research. However, the focus of the recommendations should be on the clinical implications, which supports to include this criterion. All Task Force members agreed unanimously on this (21/21 agreed).

Box 1 EULAR definition of difficult-to-treat RA

1. Treatment according to European League Against Rheumatism recommendation and failure of ≥2 b/tsDMARDs (with different mechanisms of action)* after failing csDMARD therapy (unless contraindicated).†
2. Signs suggestive of active/progressive disease, defined as ≥1 of:
   a. At least moderate disease activity (according to validated composite measures including joint counts, for example, DAS28-ESR>3.2 or CDAI>10).
   b. Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other).
   c. Inability to taper glucocorticoid treatment (below 7.5 mg/day prednisone or equivalent).
   d. Rapid radiographic progression (with or without signs of active disease).‡
   e. Well-controlled disease according to above standards, but still having RA symptoms that are causing a reduction in quality of life.
3. The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient.

All three criteria need to be present in D2T RA.
b, biological; CDAI, clinical disease activity index; cs, conventional synthetic; DAS28-ESR, disease activity score assessing 28 joints using erythrocyte sedimentation rate; DMARD, disease-modifying antirheumatic drug; mg, milligram; RA, rheumatoid arthritis; ts, targeted synthetic.
*Unless restricted by access to treatment due to socioeconomic factors.
†If csDMARD treatment is contraindicated, failure of ≥2 b/tsDMARDs with different mechanisms of action is sufficient.
‡Rapid radiographic progression: change in van der Heijde-modified Sharp score ≥5 points at 1 year.[16]

Order

Most Task Force members agreed to start the definition with the treatment failure history criterion instead of the characterisation of active/symptomatic disease. However, the group noted that starting with signs of active disease might be better focussed on the patients' needs. Therefore, with the agreement of all Task Force members, it was decided to vote on the order of the two criteria, by which all Task Force members supported the first version of the definition (agreed 31/31 (AH, who joined the Task Force later, did not vote), box 1).

DISCUSSION

The treatment of the heterogeneous patient population that comprises D2T RA is often a clinical challenge for which practical management recommendations are needed. Several factors may complicate the management of these patients. Such factors include persistent inflammatory activity due to resistance of disease to DMARDs, limited drug options due to adverse drug reactions and/or comorbidities that preclude the use of DMARDs or treatment non-adherence. On the other hand, concomitant

syndromes or diseases, such as fibromyalgia, osteoarthritis and psychosocial factors associated with poor coping, can result in non-inflammatory symptoms (eg, pain) that can mimic inflammatory activity and therewith contribute to D2T RA. Currently, D2T RA EULAR management recommendations are under development, aiming to cover all inflammatory and non-inflammatory factors underlying D2T RA. These will include both pharmacological and non-pharmacological treatment options and will be complementary to the existing RA recommendations.[1–3] As an essential initial step in the development of recommendations for D2T RA, the Task Force provided terminology and a definition of D2T RA.

The term 'difficult-to-treat' was selected because it was deemed to best capture the possible clinical scenarios. A definition of D2T RA, consisting of three criteria was agreed on by consensus by a multidisciplinary group of experts including patient representatives: (1) treatment failure history; (2) characterisation of active/symptomatic disease; and (3) clinical perception. These elements were selected based on the results of the survey.

The second criterion has five subelements, reflecting all potential clinically meaningful indicators of active/symptomatic disease. In this definition, in accordance with recent recommendations, the term 'moderate disease activity according to validated composite measures including joint counts' was used.[1 3] However, these indices might not always include the affected joints (eg, feet) or other signs of disease activity.[14] The 'Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other)' item covers all potentially affected joints, as well as extra-articular manifestations.

The acceptable GC dose for chronic use remains a matter of discussion, although there is a significant group of RA patients that is treated with GCs long-term. Current EULAR RA recommendations suggest to consider using GCs, when initiating or changing csDMARDs, but GCs should be tapered as rapidly as clinically feasible.[1] The EULAR Task Force in charge of evaluating the risk of long-term GC therapy suggested that the risk of harm is generally low at long-term doses of ≤5 mg prednisone equivalent per day.[15] In the currently proposed definition of D2T RA, in accordance with the result of the survey,[8] 'Inability to taper glucocorticoid treatment (below 7.5 mg/day prednisone or equivalent)' is listed as a criterion. We realise that lower GC doses were suggested by other EULAR Task Forces, on the other hand, we believe that less stringent criteria will be more realistic to define the D2T patients, as inability to follow these criteria can indicate a management problem.

The Task Force felt that not only patients fulfilling criterion 1 and 3 with inflammatory activity should be able to be classified as having D2T RA, but also those patients with non-inflammatory complaints. Coexisting non-inflammatory conditions may lead to a high clinical burden. These may mimic inflammatory activity by hampering proper grading of disease activity and 'falsely' elevating disease activity scores through rather subjective measures.[5] Additionally, these symptoms (such as fatigue or pain) could reduce quality of life. Therefore, the second criterion 'Signs suggestive of active/progressive disease' was deemed to cover the wide variety of patients with inflammatory activity and/or non-inflammatory complaints.

There are some limitations of this work. The definition of D2T RA needs to be validated. Rheumatologists' and patients' acceptance can, as a first step, be used as a sign of face validity. Furthermore, not all aspects of D2T RA may have been adequately captured by the currently proposed definition, although the criteria mentioned are agreed on by a large group of experts based on a survey involving >400 rheumatologists. A further complicating factor might be that, as also apparent from the definition, this patient group is rather heterogeneous and hence difficult to capture in one definition.

In conclusion, the principal goal of RA management is to achieve sustained remission or at least low disease activity following steps of the current EULAR recommendations.[1] A new management approach is necessary for D2T RA patients, in which this treatment goal is not achieved. Hopefully, the definition presented here will provide a robust and consistent identification of patients with D2T RA. In addition, this definition can provide a platform to define a group of similar patients for research. Further work is underway to provide detailed recommendations for the management of D2T RA.

Author affiliations
[1]Department of Rheumatology, 3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary
[2]Department of Genetics, Cell and Immunobiology, Semmelweis University, Budapest, Hungary
[3]Department of Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[4]Department of Rheumatology, Bács-Kiskun County Hospital, Kecskemét, Hungary
[5]Department of Rheumatology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
[6]Department of Rheumatology, Meander Medical Center, Amersfoort, the Netherlands
[7]Salisbury Foundation Trust NHS Hospital, Wiltshire, UK
[8]EULAR Standing Committee of People with Arthritis/Rheumatism in Europe (PARE), Zurich, Switzerland
[9]Department of Rheumatology, 1st Faculty of Medicine, Charles University and Institute of Rheumatology, Prague, Czech Republic
[10]CREATE Centre, Section of Rheumatology, School of Medicine, Division of Infection and Immunity, Cardiff University, Cardiff, UK
[11]Université de Paris Department of Rheumatology - Hôpital Cochin. Assistance Publique - Hôpitaux de Paris INSERM (U1153): Clinical epidemiology and biostatistics, PRES Sorbonne Paris-Cité, Paris, France
[12]Department of Psychology, Utrecht University, Utrecht, the Netherlands
[13]Epidemiology Unit, German Rheumatism Research Centre, and Rheumatology, Charité, University Medicine, Berlin, Germany
[14]Department of Internal Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria
[15]Department of Rheumatology, Bravis Hospital, Roosendaal, the Netherlands
[16]Department of Rheumatic Diseases, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands
[17]Department of Pharmacy, Paris Descartes University, Hôpital Cochin, Assistance Publique Hôpitaux de Paris, Paris, France
[18]School of Health and Society, Centre for Health Sciences Research, University of Salford, Salford, UK
[19]Centre for Rheumatic Diseases, King's College London, London, UK
[20]School of Medicine, Catholic University of the Sacred Heart, Rome, Italy
[21]Department of Internal Medicine 3, Rheumatology and Immunology, Friedrich-Alexander University of Erlangen-Nuremberg and Universitatsklinikum Erlangen, Erlangen, Germany
[22]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
[23]Centre for Musculoskeletal Research, School of Biological Sciences, Faculty of Biology, Medicine & Health, University of Manchester, Manchester, UK
[24]Department of Rheumatology and Clinical Immunology, Justus-Liebig University Giessen, Kerckhoff Clinic Bad Nauheim, Bad Nauheim, Germany
[25]Leeds Institute of Rheumatic & Musculoskeletal Medicine, University of Leeds, Leeds, UK
[26]Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK
[27]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands

Twitter Yeliz Prior @YelizPrior and Elena Nikiphorou @ElenaNikiUK

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ORCID iDs
György Nagy http://orcid.org/0000-0003-1198-3228
Nadia MT Roodenrijs http://orcid.org/0000-0002-4364-3183
Melinda Kedves http://orcid.org/0000-0002-9271-5024
Zoltan Szekanecz http://orcid.org/0000-0002-7794-6844
Johannes WG Jacobs http://orcid.org/0000-0002-7438-3468
Daniel Aletaha http://orcid.org/0000-0003-2108-0030
Elena Nikiphorou http://orcid.org/0000-0001-6847-3726
Gianfranco Ferraccioli http://orcid.org/0000-0002-6884-4301
Georg Schett http://orcid.org/0000-0001-8740-9615
Maya H Buch http://orcid.org/0000-0002-8962-5642
Désirée van der Heijde http://orcid.org/0000-0002-5781-158X

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EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy with checkpoint inhibitors

Marie Kostine ,[1] Axel Finckh ,[2] Clifton O Bingham 3rd,[3] Karen Visser,[4] Jan Leipe,[5,6] Hendrik Schulze-Koops,[6] Ernest H Choy,[7] Karolina Benesova,[8] Timothy R D J Radstake,[9] Andrew P Cope,[10] Olivier Lambotte,[11] Jacques-Eric Gottenberg ,[12] Yves Allenbach ,[13] Marianne Visser,[14] Cindy Rusthoven,[14] Lone Thomasen,[15] Shahin Jamal,[16] Aurélien Marabelle,[17] James Larkin,[18] John B A G Haanen,[19] Leonard H Calabrese ,[20] Xavier Mariette,[21,22] Thierry Schaeverbeke[1]

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For numbered affiliations see end of article.

Correspondence to
Dr Marie Kostine, Rheumatology, Centre Hospitalier Universitaire de Bordeaux Groupe hospitalier Pellegrin, Bordeaux 33000, France;
marie.kostine@chu-bordeaux.fr

XM and TS are joint senior authors.

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ABSTRACT

Background Rheumatic and musculoskeletal immune-related adverse events (irAEs) are observed in about 10% of patients with cancer receiving checkpoint inhibitors (CPIs). Given the recent emergence of these events and the lack of guidance for rheumatologists addressing them, a European League Against Rheumatism task force was convened to harmonise expert opinion regarding their identification and management.

Methods First, the group formulated research questions for a systematic literature review. Then, based on literature and using a consensus procedure, 4 overarching principles and 10 points to consider were developed.

Results The overarching principles defined the role of rheumatologists in the management of irAEs, highlighting the shared decision-making process between patients, oncologists and rheumatologists. The points to consider inform rheumatologists on the wide spectrum of musculoskeletal irAEs, not fulfilling usual classification criteria of rheumatic diseases, and their differential diagnoses. Early referral and facilitated access to rheumatologist are recommended, to document the target organ inflammation. Regarding therapeutic, three treatment escalations were defined: (1) local/systemic glucocorticoids if symptoms are not controlled by symptomatic treatment, then tapered to the lowest efficient dose, (2) conventional synthetic disease-modifying antirheumatic drugs, in case of inadequate response to glucocorticoids or for steroid sparing and (3) biological disease-modifying antirheumatic drugs, for severe or refractory irAEs. A warning has been made on severe myositis, a life-threatening situation, requiring high dose of glucocorticoids and close monitoring. For patients with pre-existing rheumatic disease, baseline immunosuppressive regimen should be kept at the lowest efficient dose before starting immunotherapies.

Conclusion These statements provide guidance on diagnosis and management of rheumatic irAEs and aim to support future international collaborations.

INTRODUCTION

Although the concept of immunotherapy in cancer is far from new, monoclonal antibodies targeting immunological checkpoints or 'checkpoint inhibitors' (CPIs) represent a growing class of agents across multiple tumour types and at all stages of disease. Agents targeting the T-cell cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or the programmed cell death-(ligand) 1 (PD-1/PD-L1) coinhibitory receptors marked a turning point in the success of immunotherapeutic approaches.[1–3] By enhancing antitumour T-cell activity, unprecedented long-lasting tumour responses were observed in patients with unresectable or advanced metastatic disease.[4–7] The clinical value of these immune CPIs, as single agents or in combination, is being investigated in various solid tumours and haematological malignancies, and their use is expanding rapidly.[8] So far, the Food and Drug Administration and the European Medicines Agency approved seven immune checkpoint-blocking antibodies in selected cancers: one anti-CTLA-4 (ipilimumab), three anti-PD-1 (nivolumab, pembrolizumab and cemiplimab) and three anti-PD-L1 (atezolizumab, avelumab and durvalumab).

The T-cell activation induced by CPIs commonly promotes inflammatory or autoimmune-like side effects, known as immune-related adverse events (irAEs).[9] Compared with conventional cancer therapies, this spectrum of toxicities is unique and can affect any organ system, most frequently the skin, gastrointestinal tract, endocrine glands and lung. Among irAEs, specific rheumatic manifestations have been described rather rarely in randomised clinical trials, but are much more common in clinical practice. The clinical features of rheumatic irAEs have been described in a growing number of case series and reports.[10] However, despite the growing interest for irAEs among rheumatologists, evidence is lacking for the optimal diagnostic approach and the management of these patients in ways that also permit effective antitumour therapy to continue. According to a recent survey, a large proportion of

rheumatologists have limited experience and little confidence in managing rheumatic irAEs, highlighting the need for education and recommendations in this emerging condition.[11]

In 2017, the European Society for Medical Oncology developed clinical guidelines for the management of immune toxicities and mentioned the paucity of literature on management of rheumatic irAEs.[12] Three other consensus recommendations have been proposed by the Society for Immunotherapy of Cancer, the American Society of Clinical Oncology and The National Comprehensive Cancer Network, which among others included the management of inflammatory arthritis, polymyalgia rheumatica and myositis.[13–15] This European League Against Rheumatism initiative assembled international experts primarily from the rheumatology and immunology but also the oncology field with the explicit goal of generating the first set of recommendations for the diagnosis and the management of rheumatic irAEs arising as a direct consequence of CPI. Rheumatologists, but also in some countries internists and immunologists, have to play a pivotal role in developing with the oncologists a patient-centred approach to improve the management of rheumatic irAEs. While the initiative primarily set out to guide clinicians, it is noteworthy that there is limited and rapidly changing literature and that future additional studies can drastically change the profile for diagnosis and management. This area will be a continually evolving field; therefore, the accompanying comments may also serve as a framework for future longitudinal cohorts and/or clinical studies.

METHODS

After approval by the European League Against Rheumatism Executive Committee, an international task force was convened to develop points to consider for the diagnosis and the management of rheumatic irAEs due to cancer immunotherapy. Among these members, were 19 clinical experts from Europe and North America (14 rheumatologists including 2 delegates of the European League Against Rheumatism young rheumatologists' network EMEUNET, 2 internists and 3 oncologists), 1 clinical epidemiologist, 1 allied health professional and 2 patient representatives from the PARE network of patient research partners. The process adhered to the updated European League Against Rheumatism standardised operating procedures for the development of recommendations.[16]

In July 2018, the first meeting was convened in Zürich, Switzerland, to define the focus of the task force, identify the target population and the research questions for the systematic literature review (SLR). The SLR was performed by the research fellow (MK), with support from the clinical epidemiologist (AF) and a librarian (Catherine Weill), to identify relevant publications through December 2018. Based on the findings of the SLR, a first draft of points to consider including 12 items was prepared by the fellow (MK) and the two convenors (TS and XM).

SLR results were presented at a second meeting that was held in Zürich, Switzerland, in January 2019. Following the evaluation of literature and a group discussion of the first draft of propositions, the task force formulated overarching principles and consensus statements. Each proposal was then submitted to a voting process, requiring at least 75% of votes in the first ballot for each recommendation to be accepted. In case this threshold was not achieved, further discussion and textual changes were proposed for a second round, for which a 67% majority was required. Five members of the task force could not attend this second meeting, but they subsequently commented and voted on each statement by email. The level of evidence (LoE) and grade of recommendation was based on the Oxford Levels of Evidence.[17] After this second face-to-face meeting, members of the task force were asked to anonymously rate each item in an online survey, on a scale of 0 (absolutely disagree) to 10 (absolutely agree) to assess the level of agreement (LoA). Furthermore, the task force agreed on adding relevant references published between the SLR and the writing of this manuscript. The manuscript was reviewed and approved by all task force members and the European League Against Rheumatism Executive Committee before submission.

RESULTS

Systematic literature review

The literature search strategy and summary of results are detailed in online supplementary data. The first objective was to identify phase III clinical trials to assess the frequency and type of rheumatic and musculoskeletal diseases' (RMDs) complaints associated with CPI compared with the comparator group. The search was performed using Medline, Embase and the Cochrane Library, through December 2018. Among 630 references identified, 22 studies were selected for inclusion. The second objective was to obtain detailed information on rheumatic and musculoskeletal symptoms that have been described under CPI treatment. The third objective was to assess outcomes in patients with pre-existing autoimmune diseases. Therefore, relevant keywords relative to three key domains were used in Medline and Embase databases: immune CPIs, rheumatic and systemic diseases and adverse events. Abstracts from the last two European League Against Rheumatism and American College of Radiology meetings were included, combined with manual searches from references of the selected articles. From among 2156 references identified, 170 were included, including pharmacovigilance registries (n=5), case series (n=51) and case reports (n=114).

After group discussion of the results of the SLR, the consensus process was initiated and the full task force agreed on a final set of 4 overarching principles and 10 points to consider (table 1).

Overarching principles

A. Rheumatic and musculoskeletal immune-related adverse events can occur as manifestations in cancer patients receiving immunotherapy with checkpoint inhibitors (LoE na; LoA 9.6).

Analysis of phase III clinical trials revealed that arthralgia, arthritis, myalgia, myositis, dry mouth, musculoskeletal and back pain were reported in patients receiving CPI. However, their frequency was not significantly different to that of patients receiving chemotherapy or placebo.[5 18–38] Data from several series, both retrospective and prospective, reporting prevalences of rheumatic irAEs in real life, ranging from 1.5% to 22%, suggest that rheumatic irAEs are under-reported in clinical trials.[39–54] Of note, an heterogeneous definition of rheumatic irAEs may explain such wide interval. Many clinical trials do not report rheumatic irAEs (by disregarding of musculoskeletal/rheumatic events as a distinct organ system, even in the online supplementary data) or partially only report high-grade and/or frequent adverse events (ie, occurring in ≥10% of the patients). Therefore, the task force wanted to emphasise with this first principle that rheumatic and musculoskeletal manifestations are a relevant part of the broad spectrum of irAEs.

B. Management of rheumatic and musculoskeletal immune-related adverse events should be based on a shared decision-making process between patients, oncologists and rheumatologists (LoE na; LoA 9.5).

Table 1 Overarching principles and points to consider for the diagnosis and management of rheumatic irAEs

		LoE	GoR	LoA (0–10) mean (SD)
Overarching principles				
A.	Rheumatic and musculoskeletal immune-related adverse events can occur as manifestations in cancer patients receiving immunotherapy with checkpoint inhibitors.	n.a.	n.a.	9.6 (0.7)
B.	Management of rheumatic and musculoskeletal immune-related adverse events should be based on a shared decision-making process between patients, oncologists and rheumatologists.	n.a.	n.a.	9.5 (1.1)
C.	Rheumatologists should engage with oncologists to contribute to the inter-disciplinary care of patients presenting with musculoskeletal signs and symptoms.	n.a.	n.a.	9.1 (1.2)
D.	The role of rheumatologists is to assist oncologists in differential diagnosis and to relieve rheumatic and musculoskeletal symptoms to an acceptable level enabling patients to maintain effective cancer immunotherapy.	n.a.	n.a.	9.5 (0.9)
Points to consider				
1.	Rheumatologists should be aware of the wide spectrum of clinical presentations of rheumatic and/or systemic immune-related adverse events that often do not fulfil traditional classification criteria of RMDs.	4	C	9.5 (1.2)
2.	Oncologists should be encouraged to consult rheumatologists promptly for assessment when rheumatic musculoskeletal and systemic signs or symptoms are suspected due to immunotherapy, and rheumatologists should provide facilitated access for such patients.	5	D	9.4 (1.3)
3.	Metastases, paraneoplastic syndromes and unrelated rheumatic diseases should be considered as a potential differential diagnosis of rheumatic immune-related events. The comprehensive assessment should be focused on documenting evidence of target organ inflammation, and based on history, clinical features, laboratory tests, imaging and/or biopsy.	4	C	9.5 (0.9)
4.	In case of inefficacy of symptomatic treatment and depending on the disease severity, local and/or systemic glucocorticoids should be considered for immune-related rheumatic and systemic symptoms. Dose regimen and route of administration should be decided according to the clinical entity and activity. When improvement is achieved, systemic glucocorticoids should be tapered to the lowest effective dose to control the symptoms.	4	C	9.4 (1)
5.	csDMARD should be considered in patients with insufficient response to acceptable dose of glucocorticoids or requiring glucocorticoid-sparing.	4	C	9 (1.2)
6.	For patients experiencing severe immune-related rheumatic and systemic immune-related adverse events or with insufficient response to csDMARD, bDMARD may be considered, with TNF or IL-6 inhibitors being the preferred options for inflammatory arthritis.	4	C	8.8 (1.2)
7.	The decision to hold or to continue the cancer immunotherapy should be based on the severity of rheumatic immune-related adverse events, the extent of required immunosuppressive regimen, the tumour response and its duration, as well as the future oncology treatment plan, in a shared decision with the patient.	5	D	9.4 (1)
8.	Myositis may be a severe condition. Immunotherapy withdrawal needs to be discussed. In the presence of life-threatening manifestations (bulbar symptoms (dysphagia, dysarthria, dysphonia), dyspnoea and myocarditis), high dose of glucocorticoids, IVIg and/or plasma exchange should be considered; immunotherapy withdrawal is always necessary.	4	C	8.9 (1.2)
9.	A pre-existing autoimmune rheumatic and/or systemic disease should not preclude the use of cancer immunotherapy. Baseline immunosuppressive regimen should be kept at the lowest dose possible (for glucocorticoids, below 10 mg prednisone per day if possible). However, many patients may have a flare of the underlying condition and/or immune-related adverse events, requiring the use of glucocorticoids and/or DMARDs.	4	C	9 (1.3)
10.	Before initiation of cancer immunotherapy, there is no indication to test every patient for the presence of autoantibodies. In the case of unexplained rheumatic, musculoskeletal or systemic symptoms, a complete rheumatological assessment should be performed.	5	D	9 (1.3)

GoR: A: based on consistent level 1 studies; B: based on consistent level 2 or 3 studies or extrapolations from level 1 studies; C: based on level 4 studies or extrapolations from level 2 or 3 studies; D: based on level 5 studies or on troublingly inconsistent or inconclusive studies of any level.
LoE: 1a: systematic review of RCTs; 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including 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'.
bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug; GoR, grade of recommendation; IL-6, interleukin 6; irAEs, immune-related adverse events; IVIg, intravenous immunoglobulin; LoA, level of agreement; LoE, level of evidence; RCT, randomised clinical trial; RMD, rheumatic and musculoskeletal disease; TNF, tumour necrosis factor.

Rheumatic and musculoskeletal irAEs occur in a context of cancer; therefore, a dialogue between rheumatologists and oncologists is important to balance the harm and risk of oncology treatment and immunosuppressive drugs. The most important stakeholder is the patient. Shared decision between a patient and his/her rheumatologist is a fundamental principle of RMDs management, as illustrated by its representation as an overarching principle in several European League Against Rheumatism recommendations.[55–57] Because evidence-based data for irAEs management are limited, and irAEs can have a large impact on the quality of life, patient's preferences and discussions concerning risks and benefits of each treatment option are even more important.

C. Rheumatologists should engage with oncologists to contribute to the inter-disciplinary care of patients presenting with musculoskeletal signs and symptoms (LoE na; LoA 9.1).

IrAEs may affect any organ system including the rheumatic and musculoskeletal system. Some patients may even experience multiple organ toxicities in sequence or concurrently. The importance of developing a local multidisciplinary network of oncologists and specialists of all organ system potentially involved in the management of irAEs has been recently highlighted.[58 59] Rheumatologists should actively engage in these local multidisciplinary networks as valuable members due to their knowledge of clinical immunology, their expertise in multiorgan autoimmune disease and their long-standing

experience with the use of immunosuppressive drugs and biological therapies.[60] This engagement should also include efforts aimed at improving patient education before or when starting cancer immunotherapy, to prevent delay in diagnosis when rheumatic or musculoskeletal side effects occur. Patients have reported that they were informed about other immune-related side effects more than rheumatic or musculoskeletal symptoms.[61] Furthermore, since the rheumatic and the cancer disease both induce high impact on the patient's life, even when independently considered and when disease activity is controlled (ie, fatigue, pain, functional impairments, emotional problems, secondary effects of the treatments), the value of an interdisciplinary collaboration between the rheumatologist and the oncologist is worthwhile.

D. The role of rheumatologists is to assist oncologists in establishing the diagnosis and to relieve rheumatic and musculoskeletal symptoms to an acceptable level enabling patients to maintain effective cancer immunotherapy (LoE na; LoA 9.5).

This principle aimed to better define the role of rheumatologists as oncologists' partners based on the clinical experience of the task force members. Once a patient with cancer receiving immunotherapy is referred for evaluation of rheumatic or musculoskeletal symptoms, the rheumatologist should consider several potential aetiologies: tumour progression, paraneoplastic syndromes, non-rheumatic events (ie, viral infection, thrombosis, endocrine abnormality), all already considered by the referring oncologist, or rheumatic/systemic irAE or immune non-related adverse events. This aspect of differential diagnosis is also described in more detail in recommendation 3. Once a rheumatic irAE is diagnosed, the supervising rheumatologist should propose an appropriate treatment to relieve patient's symptoms to an acceptable level with the objective of maintaining quality of life and permitting continuation of effective cancer immunotherapy, if this is recommended by the oncologist. This treatment goal is different to classic rheumatic entities, in which usually remission is the targeted treatment outcome.

Points to consider

1. Rheumatologists should be aware of the wide spectrum of clinical presentations of rheumatic and/or systemic immune-related adverse events that often do not fulfil traditional classification criteria of RMDs (LoE 4; LoA 9.5).

While arthralgia and myalgia were the most commonly reported rheumatic irAEs in clinical trials, numerous case series and reports have captured a broader spectrum of de novo rheumatic and systemic manifestations that can occur with cancer immunotherapy.[62–64] Polymyalgia rheumatica (PMR)-like syndromes and inflammatory arthritis syndromes are two of the major clinical presentations encountered.[39–41 48 65 66] PMR-like manifestation occurred with a median exposure time to CPI of 60 days, but also much later (IQR 24–210 days). Exposure time to CPI was generally longer for patients experiencing inflammatory arthritis (median 120 days, IQR 48–262 days). In addition, a variety of other rheumatic syndromes have been reported. These include arthralgia; monoarthritis, oligoarthritis or polyarthritis; reactive arthritis; psoriatic arthritis (PsA); remitting seronegative symmetrical synovitis with pitting oedema (RS3PE); tenosynovitis; enthesitis; non-inflammatory musculoskeletal conditions and osteoarthritis.[41 44 46 51 66–77] Importantly, autoantibodies are often absent. In arthritis, only a few patients are positive for rheumatoid factor (RF; n=20, range 18–246 UI/mL) and/or anti-citrullinated peptide antibodies (ACPAs; n=14, range 18–614 U/mL).[78] Instead, positivity of antinuclear antibodies (ANAs) is observed, but often at a low titre (range 1:80 to 1:3200, one patient with ANA 1:12 800 and only 35 patients with ANA >1:160). Similarly, acute phase reactants may be normal in some patients with PMR-like presentations.[41] Overall, around 20% of patients fulfilled classification criteria of rheumatoid arthritis (RA) (55/271) or PMR (11/52). This percentage was higher (55%) for PsA (6/11), as well as in a recent series of PMR-like syndrome (37/49; 75%).[79] The first observation of recurrent pseudogout flares 7 to 10 days after each nivolumab infusion has been recently reported.[80]

Several cases of myositis have been reported, with frequent limb-girdle myalgia and weakness that may mimic a PMR-like condition.[81–83] Because it represents a potentially life-threatening complication, the task force decided to formulate a dedicated recommendation on myositis (*recommendation 8*).

Among systemic manifestations, sicca syndrome has been described early on, presenting mainly with dry mouth, and possible associated neurological symptoms in a few patients.[40 48 65 66 84–87] Two major studies on CPI-induced sicca syndrome were published in 2019 and therefore included in this manuscript. The ImmunoCancer International Registry reported on 26 patients experiencing CPI-associated sicca syndrome. This mainly included men, with frequent organ-specific autoimmune manifestations but lower prevalence of autoantibodies (52% ANA, 20% Ro/SS-A, 9% RF, 8% La/SS-B) in comparison with classical Sjögren's syndrome.[88] Interestingly, a predominant T-cell infiltrate with acinar destruction has been reported in salivary glands, distinct from the histological profile of idiopathic primary Sjögren's syndrome. Authors hypothesise that CPI therapy may break immune tolerance locally leading to the activation of cytotoxic T cells damaging the salivary epithelium.[89]

Other systemic manifestations have been described, including sarcoidosis or sarcoid-like reactions.[90–93] The diagnosis is usually suspected through imaging when new hilar lymphadenopathy or pulmonary nodules are detected in imaging, requiring biopsy. Half of patients experienced cutaneous manifestations (nodules, rash), and some patients had cough/dyspnoea (29%) and arthralgia/arthritis (18%). Uveitis, parotitis, hypercalcaemia and neurological symptoms are rarely reported. Some patients experienced systemic sclerosis or scleroderma-like reactions, all presenting with skin thickening, but only one with new-onset Raynaud's phenomenon.[48 94–96] None tested positive for specific autoantibodies. Since PD-1-deficient mice spontaneously developed lupus-like autoimmune diseases with arthritis and glomerulonephritis, such clinical phenotypes could be expected in patients treated with anti PD-(L)1 agents, but are not observed. A few cases of lupus-like cutaneous reaction and one Jaccoud arthropathy have yet been reported with anti-PD-1 agents, and only one lupus-like nephritis was attributed to anti-CTLA-4 treatment.[97–102]

All vessel-sized vasculitis (eg, large, medium and small vessels) with various clinical manifestations, including purpura, digital necrosis arthralgia, arthritis, myalgia, fever, fatigue and abdominal pain have also been reported.[40 48 84 103–113] Of note, ANA, antineutrophil cytoplasmic antibodies (ANCAs), cryoglobulin and RF were rarely positive. Analysis of the WHO pharmacovigilance database revealed that temporal arteritis (n=16) was particularly over-reported with ipilimumab monotherapy treatment.[114] The first case of granulomatosis with polyangiitis with a high anti-PR3 ANCA titre was reported in 2019.[115]

Recently, patients experiencing rapid bone loss with CPI leading to multiple fractures were reported, raising the question of a potential influence of immune activation on bone metabolism.[116]

Importantly, rheumatic and/or systemic irAEs may occur across all classes of CPI, most frequently and severely with combination treatments and may be associated with other organ-specific irAEs.

2. Oncologists should be encouraged to consult rheumatologists promptly for assessment when rheumatic musculoskeletal and systemic signs or symptoms are suspected due to immunotherapy, and rheumatologists should provide facilitated access for such patients (LoE 5; LoA 9.4).

The data that are available regarding the process of referral to a rheumatologist suggests that this is not widely done and might lead to delay in diagnosis. In one series, only 4 out of 12 patients experiencing rheumatic irAEs were reviewed by rheumatologists.[43] One cohort reported an average of 9.5±9.3 days between the counselling request and the first rheumatologist visit and 2.5±4.4 months from the start of arthralgias to the confirmation of synovitis.[67] Two other series reported a median of 34 days (range 16–210 days) and 7 days (range 1–57 days) before a rheumatology appointment.[66 117] Rheumatic side effects of CPI appear underappreciated, which probably delays proper assessment and treatment. However, as mentioned in the overarching principles, a prompt rheumatological evaluation should support rapid shared treatment decision to relieve patient symptoms, maintain a good quality of life and allow pursuing an effective cancer immunotherapy.

Currently, algorithms for irAEs management are based on the severity/grade of the irAE according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0). The first international guidelines recommended referral to a rheumatologist in the case of severe symptoms not responding to glucocorticoids (grade 3). Subsequently, prompt referral was proposed as soon as the patient experienced moderate pain associated with signs of inflammation (grade 2).[12–14] While CTCAE grading is routine for oncologists, and a requirement for clinical trials, rheumatologists are less familiar with this grading which do not accurately reflect the spectrum or severity of rheumatic or systemic manifestations (online supplementary table S1). Accordingly, the task force decided not to use the CTCAE grading system to prioritise referral but instead to recommend prompt assessment, ideally before starting glucocorticoids. For this purpose, rheumatologists should be encouraged to offer facilitated access since they may be able to avoid systemic glucocorticoids or use lower dose than oncologists to manage rheumatic toxicities.

3. Metastases, paraneoplastic syndromes and unrelated rheumatic diseases should be considered as a potential differential diagnosis of rheumatic immune-related events. The comprehensive assessment should be focused on documenting evidence of target organ inflammation, and based on history, clinical features, laboratory tests, imaging and/or biopsy (LoE 4; LoA 9.5).

The first part of this statement has previously highlighted the overarching principle of defining the role of the rheumatologist (*overarching principle D*). While delaying the diagnosis of irAEs and its adequate treatment may result in a worse prognosis regarding both CPI adherence and immune-mediated tissue/organ destruction, focusing only on irAEs without considering other differential diagnoses may also be inappropriate. CPIs are commonly administered to patients with advanced cancer, and so new rheumatic/musculoskeletal symptoms must raise suspicion of cancer progression, as well as the lack of improvement of inflammatory arthritis with glucocorticoids (ie, possibility of metastases or paraneoplastic syndrome).[118 119] Advanced imaging, such as CT scan, MRI, bone scintigraphy or positron emission tomography-CT, may be helpful in arriving at such a diagnosis. The diagnosis of irAEs versus metastasis may become even more challenging as non-malignant resorptive lesions have recently been described, which can mimic metastases.[116] Pulmonary sarcoidosis-like lesions may also be first considered as tumour progression.

Immunological toxicities may also manifest as paraneoplastic syndromes. Current literature covers mainly paraneoplastic neurological syndromes with few published data regarding paraneoplastic rheumatic syndromes.[120 121] However, based on the clinical experience of task force members, the group agreed to include paraneoplastic syndromes in the differential diagnosis of rheumatic irAEs to inform clinicians that they may encounter newly and not pre-existing paraneoplastic syndromes following CPI therapy, notably hypertrophic osteoarthropathy. RS3PE and dermatomyositis were also reported, either as paraneoplastic syndromes or induced by CPI therapy, but one may not be able to make the distinction when appearing under CPI therapy.

The term ‘unrelated rheumatic diseases’ covers manifestations for which the causal link with cancer immunotherapy is not obvious, such as shoulder tendinitis, lateral epicondylitis, non-inflammatory back pain or complex regional pain syndrome. The task force agrees that it may be difficult to establish when a specific rheumatic feature can be considered related or unrelated to the administration of CPI. Using the adverse drug reaction probability score (Naranjo scale) may help to assess the causal link with CPI therapy.

The task force proposes that the key objective of the diagnostic work-up is to document evidence of target organ inflammation. By adopting the term target organ inflammation, the task force wants to emphasise that priority for the supervising rheumatologist is not only to search for joint inflammation but also to document evidence of any organ inflammation according to the symptoms presented (muscle, fascia, vessels, heart, lung, skin, endocrine glands, salivary glands, etc), either clinically or preferably by using appropriate laboratory tests, imaging and tissue biopsy.

Tissue diagnosis should be decided on a case-by-case basis, based on the type and severity of rheumatic irAE, when other supportive information would not be sufficient to make a clinical decision in terms of therapy. Notably, histopathological data may be frequently indicated in patients presenting with vasculitis, sarcoidosis and myositis, but should not interfere with starting treatment, particularly with myositis or patients presenting with life-threatening irAE. On the other hand, synovial biopsies will not change the acute management of inflammatory arthritis. They may provide insights into targeted therapies with glucocorticoid saving approaches, but are not recommended for daily practice.

4. In case of inefficacy of symptomatic treatment and depending on the disease severity, local and/or systemic glucocorticoids should be considered for immune-related rheumatic and systemic symptoms. Dose regimen and route of administration should be decided according to the clinical entity and activity. When improvement is achieved, systemic glucocorticoids should be tapered to the lowest effective dose to control the symptoms (LoE 4; LoA 9.4).

In the absence of contraindications, symptomatic treatment including non-steroidal anti-inflammatory drugs and/or analgesics should be the initial treatment for mild-to-moderate rheumatic manifestations. There are no data on the efficacy of symptomatic therapies in the context of systemic manifestations. An anti-inflammatory effect of these drugs can be expected within several hours or a few days. Additionally, intra-articular glucocorticoids should be considered in the context of monoarthritis

or oligoarthritis, combined with an analysis of the synovial fluid, whenever possible, to rule out differential diagnoses such as infection, osteoarthritis or crystals.[40–42 48 66 67 75–77 122–126] If symptomatic treatment is insufficient and tissue inflammation is still evident, systemic glucocorticoids should be considered for both immune-related rheumatic and systemic symptoms. Overall, systemic glucocorticoids were used for 224/296 patients (76%) with arthritis[39–44 46 48 51 52 65–74 76–78 83 116 122 123 125–143] with a median dosage of 20 mg/day, for 37/65 patients (57%) with sicca syndrome[39 40 65 66 85–89] with a median dosage of 40 mg/day (16 patients for sicca symptoms, 15 patients for systemic manifestations or associated arthritis, 6 patients for sicca symptoms and associated other irAE), for 22/29 patients (76%) with vasculitis[48 84 103–106 108–112 144–150] with a median initial dosage of 60 mg/day, for 15/33 patients (45%) with sarcoidosis[39 44 91–93 151–158] with a median initial dosage of 55 mg/day, for 7/7 patients (100%) with scleroderma[48 94–96] with an initial dosage of 1 mg/kg/day and for 4/13 patients (31%) with lupus.[98–101] Subacute cutaneous lupus was mainly treated with topical steroids.[97] Treatment of patients with myositis is reported in a separate statement (*point to consider 8*).

So far, there are reassuring data regarding the use of glucocorticoids for irAE management.[159 160] For rheumatic irAEs, patients receiving glucocorticoids equivalent to 10 mg/day of prednisolone for 6 weeks concurrent to anti-PD1 therapy had a similar antitumour response.[77] However, recent preclinical data point out that glucocorticoids markedly impair the activation and the killing ability of tumour-infiltrating lymphocytes.[161] Because of concerns of glucocorticoids on antitumour responses, the task force did not recommend using methylprednisolone pulses or high-dose oral glucocorticoids in the absence of life-threatening complications and myositis, even in severe presentations, and favoured the concept of glucocorticoid sparing where rheumatologists have extensive experience with alternative options. Furthermore, the task force members recommended tapering glucocorticoids to the lowest effective dose within weeks or as soon as improvement is achieved was desirable. The objective of reaching a dose less than or equal to 10 mg/day of equivalent prednisone was considered as an acceptable target dose. This target dose as maintenance therapy is based on current preclinical and retrospective clinical data,[161–163] and higher than the one recommended for the main classical RMDs (online supplementary table S2).

5. csDMARD should be considered in patients with insufficient response to acceptable dose of glucocorticoids or requiring glucocorticoid-sparing (LoE 4; LoA 9).

In case of active rheumatic irAE requiring dose of glucocorticoids higher than 10 mg/day of equivalent prednisone, conventional synthetic disease-modifying antirheumatic drug (csDMARD) should be considered. Several csDMARDs have been used as second-line therapy in the case of an insufficient response to glucocorticoids or for use as steroid sparing agents. So far, no specific biological disease-modifying antirheumatic drug has proven superiority. For the various types of arthritis in cases reported, methotrexate was the most frequently drug prescribed, followed by hydroxychloroquine then sulfasalazine, either as monotherapy or in combination.[39–41 43 44 48 51 52 65–67 69 70 75–78 122 123 125 128 131 132 134 140–142 164 165] Of note, no safety issues were described regarding long-term use of methotrexate associated with CPI in a few patients, with a median follow-up of over 1 year.[67] It is noteworthy that a higher proportion of hypersensitivity reactions were reported with sulfasalazine in the context of CPI-induced inflammatory arthritis, suggesting caution to its use in those situations.[165] One case series reported the initiation of hydroxychloroquine prior to glucocorticoids, limiting glucocorticoid exposure, which would deserve further evaluation.[166] The use of csDMARDs has not been described for patients with CPI-induced sicca syndrome. Two patients received hydroxychloroquine and one the combination of hydroxychloroquine and methotrexate for cutaneous leucocytoclastic vasculitis.[103] One patient with granulomatosis with polyangiitis was treated with oral cyclophosphamide.[105] For other systemic manifestations, hydroxychloroquine was safely prescribed for patients with CPI-induced lupus and scleroderma and in one patient with sarcoidosis.[48 95–100 157] Four patients with scleroderma-like syndromes received mycophenolate mofetil.[48 94 96] Among them, two also received intravenous immunoglobulin. Finally, two patients with neurosarcoidosis were successfully treated with methotrexate after an infusion reaction to infliximab.[92 93]

6. For patients experiencing severe rheumatic and systemic immune-related adverse events or with insufficient response to csDMARD, bDMARD may be considered, with TNF or IL-6 inhibitors being the preferred options for inflammatory arthritis (LoE 4; LoA 8.8).

Gastroenterologists have safely and successfully administered infliximab for patients with severe CPI-induced colitis who had an insufficient response to glucocorticoids.[167 168] Based on these data, tumour necrosis factor (TNF) inhibitors (infliximab prevailing on etanercept and adalimumab) have been reported for severe and refractory inflammatory arthritis.[65 66 116 123 138] However, while patients experiencing colitis required one or two infliximab infusions, patients with arthritis may require long-term administration of TNF inhibitors, which is an important difference of unclear clinical significance at this time. A recent study reported that antitumour responses were not adversely affected in patients treated with TNF inhibitors, with a median follow-up of 9 months, but further data are needed.[169] Preclinical data support the use of TNF inhibitors, since infliximab only had a minor influence on T-cell activation and the killing ability of tumour-infiltrating lymphocytes, whereas even low doses of glucocorticoids markedly impaired this antitumour activity.[161] Furthermore, a synergistic effect of TNF inhibitors with CPI has been demonstrated in mouse models.[170 171] A phase I investigator-initiated trial (TICIMEL, NCT03293784) is currently testing the safety of this combined approach (double immunotherapy plus TNF inhibitor) in patients with melanoma. Results of this study will likely inform the management of rheumatic irAEs. The use of infliximab was also reported in two patients with neurosarcoidosis.[92 93]

There are also several observations in patients with CPI-induced inflammatory arthritis treated with tocilizumab.[48 52 68 83] Notably, one patient responded to tocilizumab after infliximab failure.[52]

Regarding interleukin 17 blockade, the use of secukinumab has been reported in a patient with mismatch-repair-deficient metastatic colon cancer and a previous history of Crohn's disease who experienced colitis, severe psoriatic rash and arthralgia.[172] While providing a dramatic relief of the immune-related skin, rheumatic and gastrointestinal side effects, subsequent tumour progression was observed. A second recent publication described the complete resolution of pembrolizumab-induced psoriasiform eruption with secukinumab in a patient with melanoma, without impact on tumour response.[173] Due to limited data and concerns about interleukin 17 inhibition on CPI efficacy, the task force agreed not to recommend interleukin 17 blockade for inflammatory arthritis.

For mechanistic reasons, abatacept should also not be considered for the treatment of CPI-induced rheumatic and systemic diseases, owing to the hypothetical risk of antagonising antitumour responses of CPI. However, one may consider its use in cases of life-threatening conditions, as discussed in the statement for myositis (*point to consider 8*).

One patient with neuro-Sjögren's syndrome was successfully treated with rituximab after intravenous pulses of methylprednisolone, immunoglobulins and one dose of cyclophosphamide.[87] Rituximab was also used in one patient with acral vasculitis without improvement and the need of surgical amputation.[105]

7. The decision to hold or to continue the cancer immunotherapy should be based on the severity of rheumatic immune-related adverse events, the extent of required immunosuppressive regimen, the tumour response and its duration, as well as the future oncology treatment plan, in a shared decision with the patient (LoE 5; LoA 9.4).

Currently, decisions regarding CPI and immunosuppressive regimens vary from institution to institution according to local practice, with no randomised trials to provide evidence in choosing between holding CPI and/or introducing an immunosuppressive regimen. Overall, the SLR revealed that CPIs were discontinued in 25% of patients experiencing inflammatory arthritis, 61% of patients with sicca syndrome (a discontinuation of CPI often due to another associated irAE), 80% of patients with vasculitis, 64% of patients with sarcoidosis, 75% of patients with scleroderma and 78% of patients with lupus. It is noteworthy that several studies reported ongoing clinical benefit in patients who discontinue their cancer immunotherapy for irAEs.[7 174 175] Well-designed prospective trials will be required help to clarify the optimal immunosuppressive regimens.

8. Myositis may be a severe condition. Immunotherapy withdrawal needs to be discussed. In the presence of life-threatening manifestations (bulbar symptoms (dysphagia, dysarthria, dysphonia), dyspnoea and myocarditis), high dose of glucocorticoids, IVIg and/or plasma exchange should be considered; immunotherapy withdrawal is always necessary (LoE 4; LoA 8.9).

Myositis belongs to the spectrum of potentially fatal toxicity associated with CPI, since it is frequently associated with myocarditis and/or myasthenia gravis.[176–178] Notably, it generally occurs very early after CPI initiation, often within the first month of treatment (median exposure time of 25 days, IQR 25–45 days). Proximal weakness and myalgia are the major symptoms, which can mimic a PMR-like condition.[81] Therefore, a high awareness for myositis is needed among rheumatologists with measurement of creatine kinase (CK) since increased CKs are seen in the majority of patients with myositis (median of 2650 IU/L, ranging from 335 to 20 270 IU/L).[48 77 81–83 100 117 179–207] Of note, CK levels are usually within the normal range in patients presenting with myalgia.[42 83] Ptosis and diplopia are also commonly reported and may be related to associated myasthenia gravis.[81 82 100 117 184 185 189 191 192 195 197 198 204 205 208–210] Of note, some patients present with dropped head syndrome.[82 198 211] Importantly, one should search for the presence of life-threatening manifestations, including dyspnoea, palpitations, chest pain or syncope, which should alert on a possible concurrent myocarditis.[39 48 77 81–83 117 177–179 182 184 185 187 190 193 200 207 211–215] Of note, an increased risk of death in patients experiencing CPI-related myositis has been observed compared with patients with idiopathic inflammatory myositis (around 20% vs less than 10%).[177 216] This increased mortality rate seems to be related to the development of myocarditis. While there is no standardised assessment of myocarditis in large series of idiopathic inflammatory myopathy, signs of myocardial inflammation cardiac has been reported on magnetic resonance tomography in more than 60% of such patients,[217] which argue that myocarditis belong to the myositis clinical spectrum and does not represent a different concomitant irAE. Therefore, cardiac evaluation must be systematic for any patient with myositis or suspected myositis. It includes cardiac troponin (troponin T is less specific than troponin I in case of associated skeletal muscle diseases) and electrocardiography. In case of clinical syndrome associated with myocarditis and/or increase cardiac troponin level and/or electrocardiography, a cardiac MRI is necessary.[218] Of note, normal cardiac enzyme cannot always rule out the possibility of myocarditis. Furthermore, the presence of bulbar symptoms (dysphagia, dysarthria, dysphonia) and/or respiratory failure may be related to myositis or associated myasthenia gravis encountered in 12.5% of patients (57/454 cases reported).[82 83 100 177 178 186 188 189 192 195 203 204 208 211 212] Of note, the majority of patients will not have a typical skin rash of dermatomyositis, only reported in a few patients.[199 201 219]

Myositis-associated autoantibodies are mostly negative, though cases with positive ANA, antistriated antibodies, anti-PM/Scl, anti-SM, anti-TIF1 gamma, anti-PL-7, anti-PL12, anti-Jo1 or anti-SRP have been reported.[77 83 117 184] Electrodiagnostic studies usually reveal myopathic pattern with musculature enhancement may be observed on MRI. Biopsy is often performed and confirms muscle damage with variable degrees of inflammatory and necrotic changes.[81] Of interest, fasciitis is also increasingly reported clinically and seen on MRI findings.[40 76 220–224]

Prompt recognition and early management of myositis is imperative. Discontinuation or at least interruption of CPI was reported in more than 85% of patients and is mandatory in the presence of dyspnoea, bulbar symptoms, severe muscle weakness and/or myocarditis. High-dose systemic glucocorticoids are the first-line treatment, usually 1–2 mg/kg/day (median dosage 70 mg/day). Ten per cent of reported patients received intravenous pulses of methylprednisolone. Up to 20% of patients also received intravenous immunoglobulins,[39 48 77 81–83 181 183–185 188 189 191 198 201 207–209 211 212 220 225 226] and plasma exchanges were performed in around 10% of patients.[48 81 82 117 150 184 188 189 191 197 204 205 226] As second-line therapy, several csDMARDs have been used: mycophenolate mofetil,[77 209 225] methotrexate,[39 44 77 81] azathioprine in one patient but stopped for pancreatitis[77] and hydroxychloroquine in one patient.[76] Six patients have been treated with infliximab, but only one successfully.[82 182 184 225] Importantly, a recent publication reported the resolution of a severe glucocorticoid-refractory myocarditis with abatacept, received after plasma exchanges was unsuccessful.[227] Another T-cell directed therapy, alemtuzumab, has been successfully used in a patient with glucocorticoid-refractory myocarditis.[228] The task force agreed that further evaluation is warranted, most notably on the impact on tumour response; however, due to the lack of effective therapy and the high mortality rate of myositis complicated with myocarditis or severe respiratory failure, one may consider their use as rescue therapy in refractory situations.

9. A pre-existing autoimmune rheumatic and/or systemic disease should not preclude the use of cancer immunotherapy. Baseline immunosuppressive regimen should be kept at the lowest dose possible (for glucocorticoids, below 10 mg prednisone per day if possible). However, many patients may have a flare of the underlying condition and/or immune-related adverse events, requiring the use of glucocorticoids and/or DMARDs (LoE 4; LoA 9).

Patients with pre-existing inflammatory or autoimmune disease have been largely excluded from clinical trials due to the theoretical risk of worsening autoimmune manifestations. However, there are several series reporting on CPI safety in such patients, with either anti-CTLA-4[229–231] or anti-PD-(L)1 .[77 232–235] Together, a flare of the pre-existing inflammatory or autoimmune disease was observed in half of patients with RA (47/86 patients), PsA (4/8 patients) and myositis (1/2 patients), 64% of patients with PMR (16/25 patients), 31% of patients with SA (4/13 patients) and patients with systemic lupus erythematosus (4/13 patients), 43% of patients with Sjögren's syndrome (3/7 patients), 25% of patients with systemic sclerosis (2/8 patients) and 20% of patients with sarcoidosis (3/15 patients), but less than 10% had to stop CPI therapy during a flare. The patient with pre-existing giant cell arteritis experienced a relapse. There was no flare reported for the few patients with pre-existing seronegative arthritis (n=4), other vasculitis (n=4) and Behçet's disease (n=1). Furthermore, 18 of 104 patients (17%) experienced other irAEs, mainly colitis (n=12), hypophysitis (n=3) and thyroiditis (n=3). One patient with RA developed myositis requiring high dose of glucocorticoids and intravenous immunoglobulins, and another patient with RA developed Sjögren's syndrome with autoantibodies (ANA 1/1280, anti-SSA and SSB). Overall, CPI was discontinued in 8% of patients with pre-existing autoimmune disease due to other irAEs, unrelated to their pre-existing autoimmune disease. In a recent case series of 112 patients with pre-existing autoimmune diseases treated with CPI, a flare of pre-existing autoimmune disease or another irAE occurred in 71% of the patients (47% has a flare of their pre-existing disease and 43% had another irAE).[236] Thus, the occurrence of a flare/irAE was frequent but mostly manageable without CPI discontinuation in 79% of the patients.

In these case series, most flares and irAEs were managed with glucocorticoids, with the need of csDMARDs in some patients, usually hydroxychloroquine, methotrexate, sulfasalazine, either in monotherapy or in combination. The need for TNF inhibitors was only reported in patients with flares of their inflammatory bowel disease flares and in two cases of new-onset colitis. Based on these data, the task force agreed that CPI therapy in patients with pre-existing autoimmune rheumatic and systemic disease was not contraindicated, provided that the patient is well-informed and closely monitored. No preventive treatment is needed. Importantly, this remains a shared decision between the oncologist, rheumatologist and the patient, and whether CPI will be used in a metastatic or adjuvant setting is a major aspect to be considered.

Regarding baseline immunosuppressive regimen, recent preclinical and clinical data highlighted the deleterious impact of baseline glucocorticoids on CPI efficacy, when used at a dosage of greater than 10 mg/day.[163 237] However, this was in patients treated with steroids for their cancer or cancer-related symptoms and not for autoimmune symptoms. Accordingly, the task force agreed on recommending the lowest immunosuppressive regimen possible at the start of CPI therapy. However, future data on prophylactic TNF inhibition and a possible synergistic effect of TNF inhibitors and CPI, reported in a mouse model and currently evaluated in patients, may challenge this statement over time.[171]

10. Before initiation of cancer immunotherapy, there is no indication to test every patient for the presence of autoantibodies. In the case of unexplained rheumatic, musculoskeletal or systemic symptoms, a complete rheumatologic assessment should be performed (LoE 5; LoA 9).

Analysis of pretreatment and post-treatment sera of anti-CTLA4-treated patients with melanoma revealed that for most autoantibodies, including RA-associated antibodies, post-treatment titres increased only marginally and were not associated with the occurrence of irAEs.[238] Similarly, the presence of ANA in serum collected prior to initiating CPI therapy was not found to predict the development of irAEs, except for colitis.[239 240] One study reported divergent data, with pre-existing antibodies independently associated with the occurrence of irAEs, but also with clinical benefits on advanced non-small cell lung cancer.[241] Notably, skin reactions were more frequent among patients with pre-existing RF.

Since autoantibodies are not found in the majority of patients experiencing CPI-induced rheumatic and systemic disease, there is no indication to test every patient at baseline. Of note, the presence of ACPAs has been detected in serum samples obtained prior to CPI therapy in few patients who experienced RA and were asymptomatic before the start of CPI.[78] But this situation might be rare, and the detection of autoantibodies in an asymptomatic patient would not preclude the start of CPI therapy. However, there is the particular situation of patients with thymoma who develop CPI-induced myositis and who all have anti-acetylcholine receptor and antistriated muscle antibodies detected in serum sample obtained prior to CPI therapy.[179] Accordingly, as myositis may evolve into a severe irAE, testing for the presence of these antibodies before starting CPI in a patient with thymoma is recommended to identify a high risk of myositis.

CONCLUSION

These points to consider provide the basis of an European League Against Rheumatism consensus on the diagnosis and the management of rheumatic and systemic irAEs which represent a new and rapidly expanding field. The task force aimed to raise awareness and to assist rheumatologists to improve the diagnosis and the management of patients with irAEs. In contrast to other irAEs, rheumatic irAEs frequently persist over time, specifically inflammatory arthritis was persistent in almost 50% at most recent follow-up with a median of 9 months in a recent study.[169] Thus, irAEs represent a new spectrum of RMDs that rheumatologists should familiarise with. Interestingly, many of these manifestations, either frequent (arthritis, myositis, sicca syndrome) or more exceptionally reported (scleroderma, lupus) are also characteristics of graft versus host disease.[242] Early consultation and strong collaboration between the referring oncologist, the treating rheumatologist, potentially other organ specialists and the patient are all required for optimal irAEs management.

These statements, being based almost entirely on low levels of evidence and on experts opinion, will undoubtedly require updating over the next few years, as new data emerge. Indeed, we expect that future oncological data will likely impact our irAEs therapeutic strategy. We also anticipate a better understanding of irAEs mechanisms and pathophysiology. Finally, multicentre collaborative efforts, prospective registries and randomised trials will help to define the optimal treatment strategies to relieve patient symptoms without altering oncological outcomes.

RESEARCH AGENDA

- To better understand pathophysiology of rheumatic and systemic irAEs.
- To develop information on rheumatic and systemic irAEs for patients starting cancer immunotherapy.
- To define optimal glucocorticoid dose and duration according to the type of rheumatic and/or systemic irAE.
- To assess the effect of different immunomodulatory/immunosuppressive agents already given before the start

of CPI therapy in pre-existing RMDs on the outcome of immunotherapy.
- To assess the effect of different immunomodulatory/immunosuppressive agents administered for de novo rheumatic and systemic irAEs on the outcome of immunotherapy, using prospective registries.
- To develop well-designed trials on irAE management.
- To assess long-term evolution of rheumatic and systemic irAEs.
- To search for predictive factors for rheumatic and systemic irAEs.
- To revise CTCAE grading of rheumatic and systemic irAEs.
- To obtain insights on the initiation and propagation of classical rheumatic diseases.

Author affiliations
[1]Rheumatology, University Hospital of Bordeaux, Bordeaux, France
[2]Division of Rheumatology, University Hospital of Geneva, Geneva, Switzerland
[3]Rheumatology, Johns Hopkins University, Baltimore, Maryland, USA
[4]Rheumatology, Haga Hospital, Den Haag, The Netherlands
[5]Department of Medicine V, Division of Rheumatology, University Hospital Centre, Mannheim, Germany
[6]Department of Internal Medicine IV, Division of Rheumatology and Clinical Immunology, University of Munich, Munich, Germany
[7]Institute of Infection and Immunity, Cardiff University School of Medicine, Cardiff, UK
[8]Rheumatology, University Hospital Heidelberg, Heidelberg, Germany
[9]Rheumatology and Clinical Immunology, Utrecht Medical Center, Utrecht, The Netherlands
[10]Academic Department of Rheumatology, King's College London, London, UK
[11]Internal Medicine and Clinical Immunology, Hopital Bicetre, Le Kremlin-Bicetre, France
[12]Rheumatology, University Hospital of Strasbourg, Strasbourg, France
[13]Internal Medicine and Clinical Immunology, Sorbonne Université, Pitié-Salpêtrière University Hospital, Paris, France
[14]EULAR PARE Patient Research Partners, Amsterdam, The Netherlands
[15]Aarhus University Hospital, Aarhus, Denmark
[16]Rheumatology, The University of British Columbia, Vancouver, British Columbia, Canada
[17]Drug Development, Gustave Roussy Cancer Center, Villejuif, France
[18]Royal Marsden Hospital NHS Foundation Trust, London, UK
[19]The Netherlands Cancer Institute, Amsterdam, Noord-Holland, The Netherlands
[20]Immunology and Rheumatology, Cleveland Clinic, Cleveland, Ohio, USA
[21]Rheumatology, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpitaux universitaires Paris-Sud – Hôpital Bicêtre, Le Kremlin Bicêtre, France
[22]3Université Paris-Sud, Center for Immunology of Viral Infections and Auto-immune Diseases (IMVA), Institut pour la Santé et la Recherche Médicale (INSERM) UMR 1184, Université Paris-Saclay, Le Kremlin Bicêtre, France

Twitter Marie Kostine @MarieKostine

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ORCID iDs
Marie Kostine http://orcid.org/0000-0002-6729-6200
Axel Finckh http://orcid.org/0000-0002-1210-4347
Jacques-Eric Gottenberg http://orcid.org/0000-0002-9469-946X
Yves Allenbach http://orcid.org/0000-0002-3185-7993
Leonard H Calabrese http://orcid.org/0000-0002-1789-4923

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EULAR recommendations for a core data set for pregnancy registries in rheumatology

Yvette Meissner ,[1] Rebecca Fischer-Betz,[2] Laura Andreoli ,[3,4] Nathalie Costedoat-Chalumeau ,[5,6] Diederik De Cock,[7] Radboud J E M Dolhain,[8] Frauke Forger,[9] Doreen Goll,[10] Anna Molto ,[11,12] Catherine Nelson-Piercy,[13,14] Rebecca Özdemir,[15] Luigi Raio,[16] Sebastian Cruz Rodríguez-García ,[17] Savino Sciascia ,[18] Marianne Wallenius,[19,20] Astrid Zbinden,[9] Angela Zink,[1] Anja Strangfeld [1]

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For numbered affiliations see end of article.

Correspondence to
Ms Yvette Meissner, Epidemiology and Health Care Research, German Rheumatism Research Center Berlin, Berlin, Berlin, Germany; y.meissner@drfz.de

YM and RF-B are joint first authors.

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ABSTRACT

Background and objective There is an urgent need for robust data on the trajectories and outcomes of pregnancies in women with inflammatory rheumatic diseases (IRD). In particular when rare outcomes or rare diseases are to be investigated, collaborative approaches are required. However, joint data analyses are often limited by the heterogeneity of the different data sources. To facilitate future research collaboration, a European League Against Rheumatism (EULAR) Task Force defined a core data set with a minimum of items to be collected by pregnancy registries in rheumatology covering the period of pregnancy and the 28-day neonatal phase in women with any underlying IRD.

Methods A stepwise process included a two-round Delphi survey and a face-to-face meeting to achieve consensus about relevant items.

Results A total of 64 multidisciplinary stakeholders from 14 different countries participated in the two rounds of the Delphi process. During the following face-to-face meeting of the EULAR Task Force, consensus was reached on 51 main items covering 'maternal information', 'pregnancy' and 'treatment'. Generic instruments for assessment are recommended for every item. Furthermore, for the five most frequent IRDs rheumatoid arthritis, spondyloarthritis, juvenile idiopathic arthritis, systemic lupus erythematosus and other connective tissue diseases, disease-specific laboratory markers and disease activity measurements are proposed.

Conclusion This is the first consensus-based core data set for prospective pregnancy registries in rheumatology. Its purpose is to stimulate and facilitate multinational collaborations that aim to increase the knowledge about pregnancy course and safety of treatment in women with IRDs during pregnancy.

INTRODUCTION

In recent years, several European pregnancy registries have been established in rheumatology to prospectively collect and analyse data on pregnant women with different inflammatory rheumatic diseases (IRD). However, certain research issues, for example, studying the pregnancy course in rare diseases, require even larger study populations, often exceeding the number of patients available in each registry, making collaborative analyses desirable. The European League Against Rheumatism (EULAR) Task Force on antirheumatic drugs during pregnancy and lactation[1] also highlighted the need for collaboration to collate data on newer medications.

Combined analysis of data from different sources requires a certain degree of homogeneity among the data collected. A recent comprehensive survey of four registries working together in the European Network of Pregnancy Registries in Rheumatology (EuNeP) showed similar study designs in terms of prospective data collection, inclusion of patients with IRD before or during early pregnancy, and reporting of data in each trimester of pregnancy.[2] However, major differences were found in the details of data collection, for example, in the instruments used to measure disease activity. As highlighted by other initiatives in rheumatology, harmonising and standardising items and their measurement across studies is critical to facilitate collaborative research.[3–6]

A EULAR Task Force was therefore convened to define a core data set for registries and observational studies that prospectively collect information about pregnant women with IRD including the neonatal phase (four weeks post partum). The core set was developed to encompass a minimum of standardised items to be collected paving the way for multinational collaborations.

METHODS

An iterative process according to EULAR standardised operating procedures was applied to develop the core set.[7] The Task Force comprised a convenor (AS) and coconvenor (RFB), a methodologist (AZi), a fellow (YM), eight Task Force members (LA, NC-C, RJEMD, FF, AM, CN-P, LR, MW), three EMEUNET members (DDC, SCRG, SS), two patient research partners (DG, RÖ) and one health professional (AZb). The scope and core areas of the core set according to the Core Outcome Set-STAndards for Development recommendations were defined by consensus.[8] A study protocol was developed and circulated among the Task Force. The flow chart gives an overview of all steps taken during the project (figure 1).

Generation of items

Items estimated relevant to be included in the core set were compiled (1) by a systematic literature

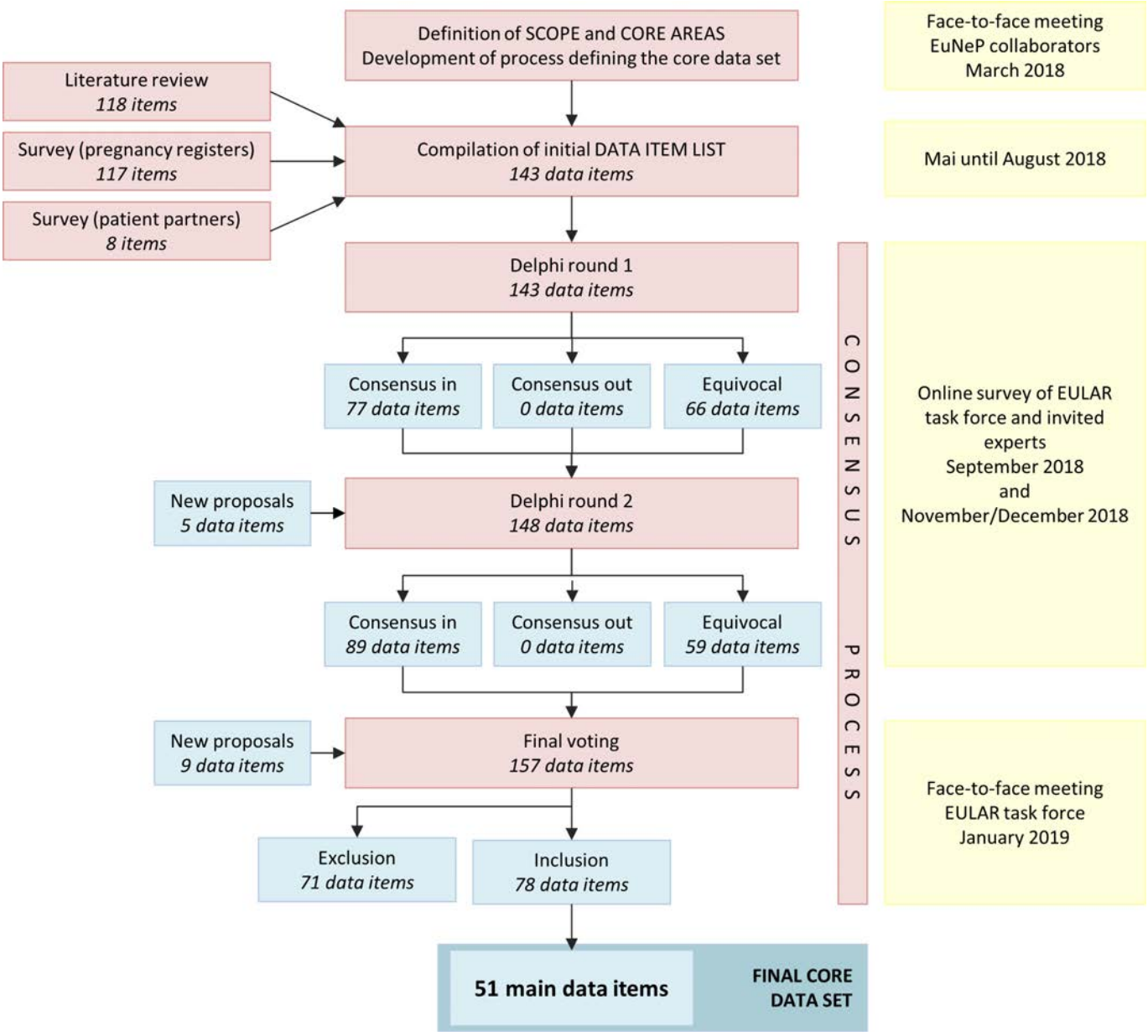

Figure 1 Flow chart of the development and consensus process for the core data set. EULAR, European League Against Rheumatism; EuNeP, European Network of Pregnancy Registries in Rheumatology

search (see online supplemental for details) and underpinned (2) by an inventory of items collected by registries participating in EuNeP[2] and (3) from results of a survey among three EuNeP patient representatives regarding their needs during pregnancy. An initial list of items was created by deleting duplicates, grouping similar items and refinement. Consequently, every item on the list was assigned to its respective core area.

Consensus process, outcome scoring and consensus definition

The importance of each item for the final core set was judged by a stepwise consensus process encompassing a two-round Delphi survey and a final vote. In addition to the members of the EULAR Task Force (except the fellow), additional experts in the field of pregnancy and rheumatology from different European countries were invited to participate during the Delphi votes. In particular, up to five clinicians involved in each of the four registries of the EuNeP collaboration, as well as clinical researchers and experts in the areas of rheumatology, epidemiology, obstetrics, gynaecology, internal medicine as well as other health professionals were directly invited by email. The Delphi process was performed using the online tool 'Delphi Manager' (http://www.comet-initiative.org/delphimanager/). This tool ensures the anonymity of all participants and adherence to the single steps of the Delphi process.

Participants were asked to rate the importance of each item to be included in a core set for pregnancy registries in rheumatology using the Grading of Recommendations, Assessment, Development and Evaluations scale[9] from 1 to 9 (1–3=not important, 4–6=important but not critical, 7–9=critical/very important). The participants had the option to indicate an item as 'unable to score' if necessary and could give comments on each item. Additionally, adding comments at the end of the survey was also possible. The scores of every participant were anonymous throughout the survey. Finally, participants were asked to suggest additional items that were not listed in the initial item list. All suggested, additional items were thoroughly reviewed by nine

Table 1 Consensus definitions

Decision	Definition	Explanation
Delphi round 1/2		
Consensus in	≥70% of the participants rated the item as critically important for the core data set (scores 7–9)	Item will be included into the final core data set
Consensus out	≥70% of the participants rated the item as not important for the core data set (scores 1–3)	Item will be excluded from the final core data set
Equivocal	All items that are neither in the consensus-in nor in the consensus-out group	No consensus was reached for the respective item. Final decision at the consensus meeting
Face-to-face consensus meeting		
Consensus in	Simple majority (>50% of votes)	Item will be included into the final core data set
Consensus out	Simple majority (>50% of votes)	Item will be excluded from the final core data set

members of the Task Force, and eligible items were added in Delphi round 2.

Every participant of Delphi round 1 was invited to rescore the items in round 2 taking total scoring results (given as percentages of all participants scoring 1–9) and their own scores of round 1 into account. Each Delphi round had to be completed within 3 weeks. After completion of both Delphi rounds, scores of round 2 were summarised and assigned to one of the three pre-specified consensus definitions comprising 'consensus in', 'consensus out' and 'equivocal' (table 1) according to OMERACT recommendations.[10]

All items that neither reached 'consensus in' nor 'consensus out' were defined as equivocal and needed a final voting. The final voting took place at a face-to-face consensus meeting of the EULAR Task Force. During this meeting the items were discussed and finally voted on. The voting was conducted via a mobile phone based electronic voting system (www.tedme.com). Items that reached a majority of votes were included into the core set, those with a majority of negative votes were excluded. Furthermore, the Task Force refined the core set and discussed all items with 'consensus-in' status regarding their applicability in a core set and usefulness for research purposes. Of note, the way of assessment of each item and their exact definition was not subject of the Delphi voting.

Since the core set is supposed to cover items important for a variety of IRDs, it was strengthened during the Task Force meeting to also define additional, disease-specific items covering laboratory markers as well as disease activity and damage measurements. All relevant items were summarised by the Task Force and the importance of each item for the respective disease was rated in a written non-anonymous voting. Each Task Force member made her/his decisions according to her/his expertise in the field. Items that reached a majority of positive votes were included in the additional item list. The additional items were defined for the most prevalent IRDs in women of reproductive age: rheumatoid arthritis, spondyloarthritis, juvenile idiopathic arthritis, systemic lupus erythematosus and other connective tissue diseases. Other connective tissue diseases include Sjögren's syndrome, undifferentiated connective tissue disease, scleroderma, myositis and mixed connective tissue diseases.

Data analysis

For both Delphi rounds, mean and SD, median, minimum and maximum as well as the distribution of scores within the three consensus categories were calculated using SAS software V.9.4.

RESULTS

Stakeholders

In total, 73 experts received an email invitation to participate in the Delphi vote, including 17 members of the EULAR Task Force. Of all experts invited, 65 (89%) participated in round 1 and 64 (88%) in round 2. About two-thirds of the experts (69%) participating in both Delphi rounds were women. The majority of participants (81%) had 10 years or more work experience, 14% were working for at least 5 and up to 10 years, and 5% indicated 5 years or less work experience. A total of 84% were rheumatologists, 5% each were obstetricians and epidemiologists, 3% each patients and midwives. Experts from 14 different European countries were represented (online supplemental table 1 shows country distribution).

Definition of core areas

Three core areas were defined as 'maternal information', 'pregnancy' and 'treatment' (figure 2). 'Maternal information' includes the core domains demographics and risk behaviours, disease characteristics of the underlying IRD and prevalent comorbidities. The core area 'pregnancy' encompasses information on obstetrical history, the course, outcomes and delivery of the current pregnancy and outcomes of the neonate. In the core area 'treatment', medical treatment within 12 months prior to conception, the treatment of the IRD during pregnancy and post partum as well as the use of other treatments during pregnancy are subsumed.

Results of the consensus process for non-disease specific items

A total of 143 items were up for voting in Delphi round 1. Of those, 77 items were voted as critically important by at least 70% of the participants. Another 69 new items were suggested to be added to the following Delphi round. All of them were thoroughly reviewed by eight members of the Task Force, and five items were considered as new and relevant for the item list (online supplemental table 2). They encompass gestational age at birth in previous pregnancies, number of previous miscarriages, neonatal infections, the use of non-steroidal anti-inflammatory drugs (NSAIDs) and start and stop dates of NSAID treatment.

With the newly suggested items of round 1, Delphi round 2 included a total of 148 items. Of those, 89 items reached consensus in during the vote, none of the items reached consensus out and 59 items were rated as equivocal and were therefore neither in nor excluded (figure 1, online supplemental table 3).

At a face to face meeting of the Task Force members (n=12), all equivocal items were voted on. Task Force members who were unable to attend the meeting (n=5) received the voting list in advance and their votes were incorporated into the decision process. Additionally, participants of the meeting discussed and evaluated all items of the final core set with respect to the importance of the item for research purposes and redundancy. All decisions are explained in detail in online supplemental table 3. In order to make the extensive list of the resulting 78 included items more comprehensible for the user, the items were consequently defined as either main item (n=51) or operationalizing item (n=27). Items of the final core set are presented in table 2. Furthermore, the way of assessment/operationalisation for each

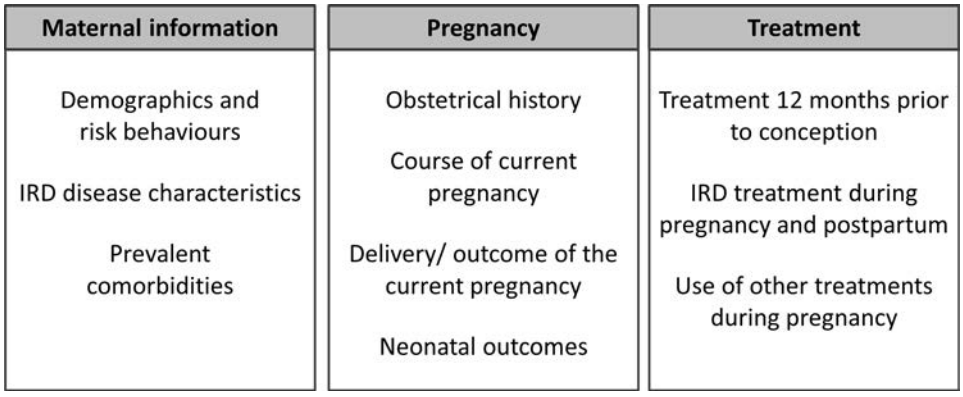

Figure 2 Core areas for the core data set for pregnancy registries in rheumatology. IRD, inflammatory rheumatic disease.

main item including instruments and categories where appropriate was defined and summarised in the online supplemental table 4.

Recommendations for disease-specific items

The recommended laboratory markers and disease activity measurements found to be relevant by the Task Force for the five IRDs rheumatoid arthritis, spondyloarthritis, juvenile idiopathic arthritis, systemic lupus erythematosus and other connective tissue diseases are presented in table 3. It is recommended for registers to collect the single components of a summary score rather than only the score, for example, C reactive protein (CRP), 28 swollen and tender joint count (SJC, TJC) rather than collecting only the disease activity score Disease Activity Score based on 28 tender and swollen joints and C reactive protein.

Methodological considerations

Pregnancy registries are prospective observational cohort studies that collect essential clinical information related to pregnancy in order to improve the safety of mother and child. The items defined with this core set refer to women with IRD and cover the pregnancy and the neonatal phase. The Task Force recommends that patients should be enrolled at the earliest possible point in time during pregnancy. Data should ideally be collected once every trimester and during the neonatal phase (within 28 days after birth). Besides the collection of items and their operationalisation, the visit date of every documented encounter between patient and physician should be reported. In addition, each registry must define, prior to its start, those diagnoses that shall be covered by the study.

DISCUSSION

We present the first consensus-based core data set for pregnancy registries in rheumatology. The comprehensive list of 51 main items should be uniformly collected by all pregnancy registries in rheumatology to ensure homogeneity and comparability of data and to enable joint utilisation of different data sources.

To date, no such recommendations for pregnancy registries in rheumatology are available even though the need has been highlighted previously.[1 11] In the absence of common standards, published pregnancy studies in rheumatology are highly heterogeneous, leading to partly controversial results[12] or non-comparable information.[13] In 2008, Schaefer *et al* summarised the objectives of pregnancy studies based on data of Teratology Information Services (TIS) and explained how they document and evaluate drug effects on pregnancy.[14] Although most of the variables are also essential for pregnancy registries in rheumatology, TIS are not tailored to patients with IRD. Since the chronic disease itself can affect the pregnancy and its outcomes,[15] it is essential to collect specific information on the disease course of IRD by registries and observational cohorts.

Recently, Vinet *et al* compiled basic lists with variables to be collected by rheumatic pregnancy registries focusing on the most important information needed to answer questions about disease activity, medication use and pregnancy outcome.[16] Many variables correspond to the herein proposed core set. However, this core set goes beyond the list of desirable information and makes recommendations on how and in what way the information should be collected in order to harmonise different data sources. In addition, the Task Force has summarised disease-specific parameters that are essential for assessing the course and severity of the IRD. Further differences can be found in methodological aspects. Vinet and colleagues followed an individual approach representing their (North American) views, while the core set is based on a structured consensus process following the methodology for EULAR recommendations. A variety of European experts in the field as well as patient representatives were involved. Registry holders and users were able to incorporate their experience into the different steps of the voting process, and the Task Force has taken the feasibility of implementing the core set in everyday clinical practice in different countries into account. International acceptance therefore can be expected to be high.

This EULAR endorsed core set represents clinically relevant and feasible parameters that are critical for scientific research, especially with a focus on multinational collaborations. The challenge of the stepwise consensus process was to select the most relevant items regarding maternal information and the rheumatic disease as well as pregnancy and neonatal outcomes. This explains the inclusion of 51 items, which is—in comparison to other core sets in rheumatology[3–5] or core sets with relation to maternal and new-born's health[17]—quite an extensive list.

The core set is a compromise between scientific purposes and research interests on the one hand and the feasibility for rheumatologists and other physicians or study nurses that document data from daily care on the other hand. We are for example aware of the importance of recording intrauterine growth restriction (IUGR) to differentiate between infants born small for gestational age (SGA) into those with a steady foetal development in rather lower percentiles of the growth curves versus those foetuses that first develop normally and then experience a sudden growth disturbance. However, we presume that information on IUGR may either be not available for many pregnancies or—since IUGR and SGA are often used interchangeably—their

Table 2 Main items of the final core data set for pregnancy registries in rheumatology and their operationalisation and instruments for assessment

No.	Main items	Operationalisation/instruments for assessment
Maternal information		
Demographics and risk behaviours		
1	Age	Date of birth or month/year of birth
2	Height	cm
3	Weight before (or in early) pregnancy	kg
4	Educational level	Highest educational level according to national standards or/total years of completed education
5	Alcohol consumption during pregnancy	Categorisation: yes/no
6	Smoking during pregnancy	Categorisation: yes/no
IRD disease characteristics		
7	IRD diagnosis	Physician reported clinical diagnosis*
8	Classification criteria	Indication, which criteria are fulfilled
9	Disease duration	Month/year or year of diagnosis
10	Physician reported IRD severity	NRS or VAS
11	Auto-antibodies†	See additional recommendations (table 3)
12	Physician reported flares	Assessment of (1) yes/no; (2) number of flares
13	Physician reported disease activity	NRS or VAS
14	Disease activity by score†	See additional recommendations (table 3)
15	C reactive protein	eg, mg/L
16	Patient reported disease activity	NRS or VAS
17	Patient reported global health	NRS or VAS
Prevalent comorbidities		
18	Selected prevalent comorbidities	Yes/no assessment of: (1) antiphospholipid syndrome, (2) diabetes mellitus, (3) arterial hypertension, (4) renal disease, (5) previous thromboembolic events
Pregnancy		
Obstetrical history		
19	Gravidity	Number
20	Parity	Number
21	Outcome of previous pregnancy(ies)	Categorised into foetal death (including pregnancy loss and stillbirths)/live birth; assessment of (1) number of foetal deaths and live births; (2) gestational age
22	Preterm birth(s)	Number
23	Neonatal death(s)	Number
24	Congenital malformations	Free text
25	Hypertensive pregnancy disorders	Yes/no assessment of: pre-eclampsia, eclampsia, HELLP syndrome
Course of current pregnancy		
26	Planned pregnancy	Yes/No
27	Assisted reproduction	Yes/No
28	Estimated date of conception	Day/Month/Year
29	Singleton/*-/multiple pregnancy	Number of foetuses
30	Adverse events of interest	(1) Yes/no assessment of non-serious and serious events of: (a) gestational hypertension, (b) pre-eclampsia, eclampsia, HELLP syndrome, (c) gestational diabetes, (d) thromboembolic events; (2) date of the beginning of the event; (3) indication if the event has led to hospitalisation or death‡
31	Other serious adverse events	Assessment of (1) the kind of event as free text; (2) date of the beginning of the event; (3) indication if the event has led to hospitalisation or death‡
Delivery/outcome of the current pregnancy		
32	Elective termination	Assessment of (1) yes/no; (2) gestational age; (3) reasons for termination categorised into (a) termination due to malformation, (b) termination due to other reasons
33	Foetal death	Including pregnancy loss and stillbirths; assessment of (1) yes/no; (2) gestational age (weeks) at diagnosis
34	Live birth	Yes/No
35	Gestational age at delivery	In weeks and days
36	Preterm premature rupture of membranes	Yes/No
37	Mode of delivery	(1) Categorised into spontaneous vaginal delivery/operative vaginal delivery/caesarean section (CS)/mode of delivery not specified, and in case of CS (2) reasons categorised into: elective CS/foetal reasons/maternal reasons/ combined foetal and maternal reasons/ unknown reasons
Neonatal outcomes		
38	Birth weight	In kilogram with two decimal digits or gram
39	Gender	Categorisation: female/male/other
40	Breast feeding	Categorisation: yes, for at least 4 weeks after birth/no
41	Congenital heart block	Yes/No
42	Congenital malformations	Free text
43	Neonatal serious adverse events during the first 28 days of live	Assessment of (1) the kind of event as free text; (2) date of the beginning of the event; (3) indication if the event has led to hospitalisation or death‡
Treatment		
Treatment 12 months prior to conception		
44	DMARD use	Assessment of (I) yes/no; (2) name§; (3) start/stop dates
45	Oral glucocorticoid use	Yes/No
46	Use of potentially teratogenic medication	Free text
IRD treatment during pregnancy and post partum		
47	DMARD use	Assessment of (1) yes/no; (2) name§; (3) dose; (4) application intervals; (5) start/stop dates; (6) reasons for discontinuation

Table 2 Continued

No.	Main items	Operationalisation/instruments for assessment
48	Oral glucocorticoid use	Assessment of (1) yes/no; (2) dose; (3) application intervals; (4) start/stop dates
49	Intraarticular glucocorticoid use	Assessment of (1) yes/no; (2) date of application
50	NSAID use	Assessment of (1) yes/no; (2) name; (3) start/stop dates
Use of other treatments during pregnancy		
51	Use of selected treatments	Yes/no assessment of use of (1) antihypertensive drugs, (2) aspirin, (3) folic acid and (4) heparin/other anticoagulants

Explanations of the main items are given in online supplemental table 4.
*Which diagnoses are covered by the registry, must defined in advance by every registry.
†Variables differ according to IRD diagnosis and are further defined in table 3.
‡This recommendation is based on the ICH E2A guideline.[25]
§For biological or targeted synthetic disease modifying antirheumatic drugs it is recommended to record the trade name.
DMARD, disease modifying anti-rheumatic drug; HELLP, complication of pregnancy characterised by haemolysis, elevated liver enzymes and a low platelet count; IRD, inflammatory rheumatic disease; NRS, Numeric Rating Scale; NSAID, non-steroidal anti-inflammatory drug; VAS, Visual Analogue Scale.

different meaning may not always be clear. We therefore decided to exclude IUGR from the core set.

The supplemental material contains descriptions and definitions for all main items as far as this is possible. Even though it would be desirable to have uniform definitions for all items, this is not feasible for various reasons. Registries can only collect data within the framework of the health system and regulatory requirements of their country of origin and therefore, country-specific differences cannot be avoided.[18 19] For a number of items, the reporting health professional has to rely on information that is provided by obstetricians, for example, the event of pre-eclampsia. Definition and classification systems however vary and can result in discrepancies of incidence rates.[20 21]

The period we were focused on for these recommendations was the time of pregnancy and the 28-day postpartum period (neonatal phase). The targeted patient population are patients with IRD. Since these recommendations shall be applicable to all IRDs, the final core set encompasses non-disease specific, generic items. Furthermore, for the five most prevalent IRDs, important laboratory markers and instruments to measure disease activity and damage have been defined. Of note, the core data set encompasses only the minimum items that have been classified as essential by experts in the field. It is up to each individual registry to add further items, to ask more details for an item and/or to use additional instruments or categories beyond those that are proposed within this core set.

Our proposed core set is on one side intended to serve as a basis for evolving registries to prioritise and facilitate data collection. On the other side, the core set can be used by existing observational studies and registries to focus their data quality management on those outcomes that were found to be of high importance to facilitate collaborative analyses with other registries. This will enable the growing number of (pregnancy) registries in Europe to perform joint analyses, allowing to explore relevant aspects in more detail and with robust data.

Collecting data in different countries by applying an internationally standardised protocol offers the chance to create the world's largest source of information of pregnancies in women with IRD including drug safety. Encouraging and recruiting pregnant patients and collecting reliable data is the basis to fill current knowledge gaps and to guide IRD patients with the wish to have children in the future. Such a database can also serve as an information source for regulatory authorities and can help

Table 3 Additional items for selected diseases

Disease	Autoantibodies/laboratory markers	Disease activity/ damage scores
Rheumatoid arthritis	► Anti-citrullinated protein antibody (ACPA) ► Rheumatoid factor (RF)	► 28 SJC ► 28 TJC ► DAS28-CRP3
Spondyloarthritis	► HLA-B27	► ASDAS ► BASDAI
Juvenile idiopathic arthritis	► Anti-citrullinated protein antibody (ACPA) ► Rheumatoid factor (RF) ► Antinuclear antibodies (ANA)	► 28 SJC ► 28 TJC ► DAS28-CRP3
Systemic lupus erythematosus	► Antiphospholipid antibodies (aPL), in particular: anti-cardiolipin (aCL) antibodies, anti-beta-2-glycoprotein-I-antibodies, lupus anticoagulant (LA) ► Antinuclear antibodies (ANA) ► Anti-double-stranded DNA antibodies ► Extractable nuclear antigen (ENA) antibodies, in particular: anti-La/SSB antibodies, anti-Ro/SSA antibodies, anti-Sm antibodies, anti-U1-ribonucleoprotein (RNP) antibodies ► Serum C3/C4	► SLEPDAI (SLEDAI*) ► SLICC/ACR damage index
Other connective tissue diseases	► Antiphospholipid antibodies (aPL), in particular: anti-cardiolipin (aCL) antibodies, anti-beta-2-glycoprotein-I-antibodies, lupus anticoagulant (LA) ► Extractable nuclear antigen (ENA) antibodies, in particular: anti-La/SSB antibodies, anti-Ro/SSA antibodies, anti-U1-ribonucleoprotein (RNP) antibodies ► Antinuclear antibodies (ANA) ► Serum C3/C4	

*SLEDAI instead of SLEPDAI for postpartum disease activity.
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DAS28-CRP3, Disease Activity Score based on 28 tender and swollen joints and C reactive protein; SLICC/ACR Damage Index, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SJC, swollen joint count; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLEPDAI, Systemic Lupus Erythematosus in Pregnancy Disease Activity Index; TJC, tender joint count.

to establish research guidelines. With this core set, we hope to encourage other scientist to set up pregnancy registries and to collaborate in joint projects.

Strengths and limitations

The methodological strength of developing this core set is the application of robust methods with a stepwise consensus-based process[7 8 22 23] involving multi-stakeholder groups, for example, experienced rheumatologists, epidemiologists, obstetricians, healthcare professionals and patients. The Delphi process is an established method for achieving consensus[24] and has the advantage of maintaining the anonymity of participants. We had a low attrition rate with only one participant who did not complete both rounds. In all consensus steps, the participants were reminded that only those items that are both essentially important for joint research and feasible in daily clinical care, should be selected.

This core data set focuses on data collection during pregnancy including the outcome of pregnancy. This decision was made in order to achieve a minimal data set for the most important time period. However, information about the time before pregnancy and further observation of women and children after delivery is highly desirable in order to answer research questions like, for example, the time to pregnancy, early abortion/miscarriage rates or the development of the child beyond 4 weeks of age. We therefore recommend to extend the observation of the child beyond the time frame addressed here in order to assess long-term outcomes concerning child development. This is a gap in the current literature and should be the focus of future collaborative studies with paediatricians.

CONCLUSION

This EULAR Task Force proposes a core data set with a minimum of items to be collected by pregnancy registries in rheumatology. Our aim was to facilitate collaborative research and joint data analyses. As the design of registries may vary considerably between countries and will be influenced by the different healthcare systems, this common data set was deliberately kept short and simple, concentrating on the most important information that is needed for meaningful joint analyses. We hope that this proposal will be useful when establishing new registries and also increase the willingness of rheumatologists, other healthcare professionals and patients to contribute to the registries and provide the necessary data.

Author affiliations
[1]Epidemiology and Health Care Research, German Rheumatism Research Center Berlin, Berlin, Germany
[2]Department for Rheumatology and Hiller Research Institute, Heinrich Heine University Düsseldorf, Dusseldorf, Germany
[3]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
[4]Unit of Rheumatology and Clinical Immunology, ASST Spedali Civili di Brescia, Brescia, Italy
[5]Internal Medicine Department, Referral Center for Rare Autoimmune and Systemic Diseases, Hospital Cochin, Paris, France
[6]CRESS, INSERM, INRA, Université de Paris, Paris, France
[7]Department of Development and Regeneration KU, KU Leuven, Leuven, Belgium
[8]Medical Centre, Department of Rheumatology, Erasmus University Rotterdam, Rotterdam, Netherlands
[9]Department of Rheumatology, Immunology and Allergology, Inselspital University Hospital Bern, Bern, Switzerland
[10]Patient research partner, Berlin, Germany
[11]Rheumatology Department, Hospital Cochin, Paris, France
[12]U-1153, INSERM, University of Paris, Paris, France
[13]Obstetric Medicine Service, Queen Charlotte's and Chelsea Hospital, London, UK
[14]Department of Women and Children's Health, Guy's and St Thomas' NHS Foundation Trust, London, UK
[15]Patient research partner, Duisburg, Germany
[16]Department of Obstetrics and Gynaecology, Inselspital University Hospital Bern, Bern, Switzerland
[17]Rheumatology Department, Hospital Universitario de la Princesa, Madrid, Spain
[18]Dipartimento di Malattie Rare, Immunologiche, Ematologiche ed Immunoematologiche. Centro di Ricerche di Immunopatologia e Documentazione su Malattie Rare (CMID). Struttura Complessa a Direzione Universitaria di Immunologia Clinica, Ospedale Torino Nord Emergenza San G. Bosco ed Università di Torino, Torino, Italy
[19]Institute of Neuromedicine and Movement Science, Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology, Trondheim, Norway
[20]Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases, Dept of Rheumatology, St Olavs Hospital University Hospital in Trondheim, Trondheim, Norway

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Twitter Laura Andreoli @lauraandreoli80, Diederik De Cock @DiederikDeCock, Anna Molto @annamolto, Catherine Nelson-Piercy @nelson_piercy and Sebastian Cruz Rodríguez-García @sdlcrodriguez

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Collaborators Peer Aries; Sebnem Ataman; Irene Bultink; Marion Couderc; Diana Dan; David d'Cruz; Jip de Vries; Thomas Dörner; Lene Dreyer;Aline Frazier; Ruth Fritsch-Stork; James Galloway; Ian Giles; Cornelia Glaser; Gaelle Guettrot-Imbert; Isabell Haase; Karin Hellgren; Jörg Henes; Merete Hetland; Kimme Hyrich; Synøve Kalstad; Emese Kiss; Estibaliz Lazaro; Véronique le Guern; Hanns-Martin Lorenz; Juan Antonio Martínez López; Monika Oestensen; Øyvind Palm; Jose Maria Pego-Reigosa; Antonia Puchner; Klara Rosta; Guillermo Ruiz-Irastorza; Christof Schaefer; Matthias Schneider; Carina Skorpen; Susanna Späthling -Mestekemper; Christof Specker; Tone Størseth Moksnes; Bjørg Tilde Svanes Fevang; Antonio Szanto; Gabriella Szucs; Tunde Tarr; Angela Tincani; Ines von Mühlenen; Anne Voss; Corinna Weber-Schoendorfer; Jakub Zavada.

Contributors All authors listed fulfil authorship criteria. They have contributed to the task force and have been engaged in the design of the work, attended meetings, were involved in drafting the manuscript and approved the final version.

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ORCID iDs
Yvette Meissner http://orcid.org/0000-0003-0147-4112
Laura Andreoli http://orcid.org/0000-0002-9107-3218
Nathalie Costedoat-Chalumeau http://orcid.org/0000-0002-1555-9021
Anna Molto http://orcid.org/0000-0003-2246-1986
Sebastian Cruz Rodríguez-García http://orcid.org/0000-0002-7773-151X
Savino Sciascia http://orcid.org/0000-0003-1266-9441
Anja Strangfeld http://orcid.org/0000-0002-6233-022X

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2019 EULAR points to consider for non-physician health professionals to prevent and manage fragility fractures in adults 50 years or older

Jo Adams ,[1] Nicky Wilson ,[1] Emalie Hurkmans,[2] Margot Bakkers,[3] Petra Balážová,[4,5] Mark Baxter,[6] Anne-Birgitte Blavnsfeldt,[7] Karine Briot ,[8] Catharina Chiari,[9] Cyrus Cooper,[10] Razvan Gabriel Dragoi,[11] Gabriele Gäbler,[12] Willem Lems,[13] Erika Mosor,[12] Sandra Pais,[14] Cornelia Simon,[15] Paul Studenic ,[16] Simon Tilley,[6,17] Jenny de la Torre-Aboki ,[18] Tanja A Stamm [12,19]

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For numbered affiliations see end of article.

Correspondence to
Professor Tanja A Stamm, Section for Outcomes Research, Centre for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Spitalgasse 23, 1090 Vienna, Austria; tanja.stamm@meduniwien.ac.at

JA and NW contributed equally.

JA and NW are joint first authors.

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ABSTRACT

Objective To establish European League Against Rheumatism (EULAR) points to consider for non-physician health professionals to prevent and manage fragility fractures in adults 50 years or older.

Methods Points to consider were developed in accordance with EULAR standard operating procedures for EULAR-endorsed recommendations, led by an international multidisciplinary task force, including patient research partners and different health professionals from 10 European countries. Level of evidence and strength of recommendation were determined for each point to consider, and the mean level of agreement among the task force members was calculated.

Results Two overarching principles and seven points to consider were formulated based on scientific evidence and the expert opinion of the task force. The two overarching principles focus on shared decisions between patients and non-physician health professionals and involvement of different non-physician health professionals in prevention and management of fragility fractures. Four points to consider relate to prevention: identification of patients at risk of fracture, fall risk evaluation, multicomponent interventions to prevent primary fracture and discouragement of smoking and overuse of alcohol. The remaining three focus on management of fragility fractures: exercise and nutritional interventions, the organisation and coordination of multidisciplinary services for post-fracture models of care and adherence to anti-osteoporosis medicines. The mean level of agreement among the task force for the overarching principles and the points to consider ranged between 8.4 and 9.6.

Conclusion These first EULAR points to consider for non-physician health professionals to prevent and manage fragility fractures in adults 50 years or older serve to guide healthcare practice and education.

Key messages

What is already known about this subject?

- Interventions delivered by non-physician health professionals to prevent and manage fragility fractures contribute to optimal patient outcomes. They have not been sufficiently covered to date in existing European League Against Rheumatism/European Federation of National Associations of Orthopaedics and Traumatology recommendations.

What does this study add?

- This paper will guide clinical practice in Europe regarding interventions delivered by non-physician health professionals to prevent and manage fragility fractures in adults 50 years or older. Several areas described in this paper highlight the necessity for further research. Future studies could build on our findings. International and national initiatives may find our paper useful as a common European reference.
- Prevention of fragility fractures is essential for good health in older age; osteoporosis and fractures are key issues that need to be considered. Especially vulnerable patient groups, for example, frail older people, and those with cognitive impairments will benefit from European standards regarding interventions delivered by non-physician health professionals to prevent and manage osteoporotic fractures.
- Implementation will be supported by national organisations, professional and scientific societies, including patient leagues.

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INTRODUCTION

Countries across the world are facing a fragility fracture crisis.[1] Estimates suggest that by 2040 over 300 million adults age 50 years or more worldwide will be at high-risk of fragility fracture.[2] In 2017, across France, Germany, Italy, Spain, Sweden and the UK alone, there were 2.68 million new fragility fractures, costing an estimated €37.5 billion.[3] These numbers are projected to rise, such that in 2030 over 3.3 million new fractures are anticipated across the same six countries, with accompanying total fracture-related costs approximating €47.4 billion.[3]

Many fragility fractures require immediate acute fracture care and typically lead to physical disability, persistent pain, impaired quality of life and increased mortality.[4] Among those who sustain a fragility fracture, the risk of imminent subsequent

Key messages

How might this impact on clinical practice or future developments?

- Improved care delivered by non-physician health professionals to prevent and manage fragility fractures offers opportunities for better health outcomes in older people in Europe.

fracture is substantial,[5 6] highlighting the importance of primary and secondary fracture prevention.

Interventions delivered by non-physician health professionals (HPs), such as dietitians, nurses, occupational therapists, pharmacists and physiotherapists, in close collaboration with rheumatologists, orthopaedic surgeons, rehabilitation specialists and general practitioners, are important in the management of patients at high-risk of fragility fractures. Interventions by non-physician HPs include exercise and functional training, prescription of assistive devices, fall prevention programmes, nutritional supplements and education. Drug therapy is important in the prevention and management of fractures, and in some countries non-physician HPs can prescribe anti-osteoporosis medicines.[7]

The European League Against Rheumatism (EULAR) Standing Committees recognise the importance of optimising healthcare delivered by non-physician HPs to people at high-risk of fragility fractures. The EULAR/EFORT (European Federation of National Associations of Orthopaedics and Traumatology) recommendations for management of patients older than 50 years with a fragility fracture and prevention of subsequent fracture,[8] focussed primarily on physician-based interventions. Interventions delivered by non-physician HPs were not comprehensively covered. Therefore, this study aimed to establish EULAR points to consider for the prevention and management of fragility fractures by non-physician HPs to complement and extend the EULAR/EFORT recommendations. As there is considerable variation across European countries in the roles and tasks of HPs, we focussed on interventions that could potentially be delivered by non-physician HPs independent of whether specific HPs do certain interventions in a country or not.

METHODS

Points to consider were developed in accordance with up-to-date EULAR standard operating procedures for EULAR-endorsed recommendations.[9] An international multidisciplinary task force was established, comprising two patient research partners, one dietitian, one geriatrician and one nurse, three occupational therapists, two orthopaedic surgeons, four physiotherapists, one specialist in physical medicine and rehabilitation and five rheumatologists, with expertise in the management of osteoporosis and/or fragility fractures. A Delphi survey, conducted by email, was undertaken to set up and prioritise the clinical questions on a 9-point Likert-scale (scores 1 to 3 'not relevant', scores 4 to 6 'potentially relevant', scores 7 to 9 '(highly) relevant'). Thirteen questions were reduced to eight via two rounds of voting by the task force (questions scoring <4 were excluded, questions scoring >6 were included and questions scoring 4 to 6 were discussed and revised). This was followed by a systematic literature review (SLR) based on the eight clinical questions (online supplementary file 1, table 1) formulated around two linked concepts: (i) adults ≥50 years of age at high-risk of primary or secondary osteoporotic fracture and (ii) interventions delivered by non-physician HPs to prevent and manage osteoporotic fractures. High-risk of osteoporotic fracture was categorised based on bone mineral density (BMD) values for osteoporosis and osteopenia[10] and/or short-term probability of fracture (table 1). Key outcomes were fractures and falls, although BMD and risk of falling were included as surrogate endpoints.

Table 1 Categorisation of individuals at high-risk of fragility fracture

Osteopenia	T score =<-1.0 to –2.5 SD
Osteoporosis	T score =≤–2.5 SD
FRAX 10-year probability of a major* osteoporotic fracture	≥20% (age independent)
FRAX 10-year probability of hip fracture	≥3% (age independent)
FRAX NOGG threshold	40 to 90 years (age dependent)

Note: T score, unit of SD from the mean for bone mineral density compared with a healthy young adult; FRAX, Fracture Risk Assessment Tool; NOGG, National Osteoporosis Guideline Group.
FRAX intervention thresholds vary between countries.
*A clinical spine, hip, forearm or humerus fracture.

Evidence was appraised using a domain-based assessment of risk of bias for primary studies,[11] and A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2)[12] and classified using the Oxford 2011 Levels of Evidence Table[13] (online supplementary file 1, tables 2-5). Evidence was rated as: sufficient, some, insufficient and insufficient evidence to determine[14] (online supplementary file 1, table 6). The research fellow (NW), and one convenor (EH), extracted data for the SLR in close collaboration with the methodologist (TAS). This SLR has been published.[15]

The task force met for one face-to-face meeting to review the results of the SLR and formulated the points to consider; these were finalised over subsequent weeks by online discussions and circulated to all task force members for voting via email. The level of agreement for the overarching principles and each point to consider was assessed using a numerical rating scale from 0 (complete disagreement) to 10 (complete agreement). In parallel with this, research and education agendas for the non-physician HP workforce to prevent and optimally manage fragility fractures were proposed and developed via a single round of iterative online discussion among the task force.

RESULTS

Two overarching principles to underpin high quality care were supported by the task force; shared decision-making[16] and multiprofessional working. Shared decision-making is an essential component of personalised care[17] and may reduce unwarranted variation in healthcare practice,[18] while involving non-physician HPs in the treatment and management of patients at high-risk of fragility fracture widens opportunities to prevent and optimally manage fragility fractures. Currently, non-physician HPs are only sometimes involved in the organisation and delivery of care for patients at high-risk of fracture.

Seven points to consider, describing non-pharmacological interventions, were developed and are summarised in table 2, along with underpinning levels of evidence, strength of recommendations and level of agreement among task force members.

Point to consider 1: identification of patients at risk of fracture

No studies evaluating the effect of fracture risk detection by non-physician HPs were included in the SLR. Case finding people at risk of fracture can be undertaken in the first instance through identification of clinical factors (for example age, low body mass index, smoking, family fracture history, height loss ≥4 cm or a thoracic kyphosis).[19 20] Simple online assessment tools incorporating various clinical risk factors (with or without a measure of

Table 2 Overarching principles and EULAR points to consider for the prevention and management of fragility fracture by non-physician HPs

No	Overarching principles			Level of Agreement (Mean (SD))
1	**The management of patients at risk of a fragility fracture should be based on shared decision making between patients and non-physician HPs.**			9 (1.8)
2	**Non-physician HPs should be involved in the management of patients at risk of fragility fractures.**			8.4 (2.2)
No	**Point to consider**	**Level of evidence**	**Strength of recommendation**	**Level of Agreement (Mean (SD))**
	Prevention of Fragility Fractures			**Median (Range)**
1	**Identification of patients at risk of fracture**			
	Non-physician HPs should identify patients at risk of fragility fracture, ensure that the patients are offered opportunities for adequate treatment and address bone fragility in patient education.	2	B	9.06 (1.16) 9.5 (7–10)
2	**Fall risk evaluation**			
	Non-physician HPs should start with fall risk evaluation of patients at risk of fragility fracture. Patients at high-risk of falls should be assessed by non-physician HPs using an individualised approach to multi-component screening or referred to one or more non-physician HPs competent in multi-component screening.	4	C	9.61 (0.70) 10 (8 to 10)
3	**Preventive multicomponent interventions**			
	Tailored multicomponent interventions, including for example:			
	► Exercise	1 to 3	A	
	► Environmental adaptations	2	D	9.33 (0.91)
	► Nutrition	1 to 2	D	10 (8 to 10)
	► Education	2	D	
	should be offered to patients at high-risk of primary osteoporotic fracture and/or high-risk of falls			
4	**Avoidance of smoking and overuse of alcohol**			
	Smoking and overuse of alcohol should be discouraged.	1	A	9.22 (1.31) 10 (5 to 10)
No	**Point to consider**	**Level of evidence**	**Strength of recommendation**	**Level of Agreement (Mean (SD))**
	Management of Fragility Fractures			**Median (Range)**
5	**Exercise and nutritional interventions for patients who have experienced a fragility fracture**			
	Non-physician HPs should ensure that patients who have experienced a fragility fracture are given opportunities for:			
	► adequate exercise	1 to 2	A	
	► adequate nutritional intake	2	D	9.22 (0.88)
	Calcium and vitamin D intake should be discussed with the patient focussing on actual and recommended daily calcium intake, calcium and vitamin D rich foods, and the individual's risk/benefit profile for vitamin D supplementation.	1 to 2	D	9.5 (8 to 10)
6	**Organisation and coordination of multidisciplinary services**			
	Non-physician HPs should be included in orthogeriatric services, FLS and/or a coordinated, multidisciplinary post-fracture prevention programme. Patients with fragility fractures should be referred to a FLS or an adequate, coordinated, multidisciplinary post-fracture prevention programme	1 to 2		9.50 (1.10) 10 (6 to 10)
7	**Adherence to anti-osteoporosis medicines**			
	Non-physician HPs should address, monitor and support medication adherence in a structured follow-up.	2 to 3	B	8.83 (1.25) 9 (6 to 10)

EULAR, European League Against Rheumatism; FLS, fracture liaison services; HPs, health professionals.

BMD) into a fracture risk algorithm (such as the Fracture Risk Assessment Tool (FRAX),[21] Garvan[22] and QFracture[23]) are freely available in many countries[24] and recent evidence suggests that FRAX-based screening and guided management of community-dwelling older women, may reduce incident hip fractures, but not overall fractures.[25] Given the centrality of risk assessment to fracture prevention, the task force agreed that non-physician HPs should identify patients at risk of fragility fracture.

Risk identification and stratification can facilitate appropriate management, and workforce developments over recent decades have widened opportunities for non-physician HPs to manage individuals at risk of fragility fracture.[26 27] National and local practice policies and pathways can be established to support requests for laboratory testing and diagnostic investigations (such as dual-energy X-ray absorptiometry scans) by non-physician HPs, and implementation of non-medical prescribing could increase patient access to effective osteoporosis treatment.[7 27] As an example, Bowers *et al*[28] reported higher anti-fracture medicine prescription rates for women at high-risk of fragility fracture with implementation of a collaborative pharmacist-physician model of management compared with physician-only management.

Point to consider 2: fall risk evaluation

Initial assessment of risk of falls in adults at high-risk of fragility fracture should focus on key questions relating to: any history of falls within the past 12 months, fear of falling and/or feeling unsteady while walking or standing.[29] A positive response in any of these areas should be followed up with a multifactorial falls-risk assessment incorporating evaluation of gait and mobility (measured for example by the Timed Up and Go test[30]) and other relevant factors, such as balance, lower limb strength, medication, postural dizziness/hypotension, vision, mental health and cognitive capacity, footwear and environmental factors.[29] Although the evidence identified in the SLR was insufficient to

determine benefit of fall risk evaluation in adults at high-risk of fragility fracture, the task force agreed that a multifactorial falls risk assessment should be done (by one appropriately skilled HP or a number of different HPs[31]) as, when followed by multifactorial fall prevention interventions, multifactorial falls risk assessment involving non-physician HPs may reduce rate of falls in older people when compared with other approaches.[32 33]

Point to consider 3: preventative multicomponent interventions

Multicomponent interventions, including for example exercise, fall-prevention strategies and education about bone health are important in primary fragility fracture prevention. Such multicomponent interventions may reduce fall rate and positively influence bone health in older people at high-risk of fragility fracture and/or at high-risk of falls.[34–36]

Regular long-term exercise is essential for bone health.[37 38] Weight-bearing impact exercise and/or resistance training promotes strong bones and improves physical performance,[38] while exercise interventions incorporating balance and functional training reduce rate of falls and number of fallers in older people at high-risk of falls living in the community.[39]

In people with bone fragility, we found sufficient evidence that multicomponent exercise incorporating dynamic weight-bearing, strength and balance training undertaken 2 to 3 days a week for at least 10 weeks, reduces risk of falling,[40] and some evidence that multicomponent exercise undertaken for >1 year positively influences BMD.[35 41] Evidence about whole body vibration or low impact exercise is limited and insufficient to determine effect on bone health-related outcomes in people with bone fragility.[42 43]

Customised multifactorial interventions, targeting individualised fall-risk factors, may reduce the incidence in falls rate in community-dwelling older people at high-risk of falling.[32 33] One randomised controlled trial (RCT),[36] reported a reduced falls rate in participants attending fall prevention clinics in Finland who received, on average, five fall and injury prevention interventions, commonly including home hazard modification, nutrition and lifestyle advice, medicines review and strength and balance training delivered by different HPs, including nurses and physiotherapists. The incidence rate of falls per 100 person years over a 12-month period were 95 in the intervention group and 131 in the control group (incidence rate ratio 0.72, 95% CI 0.61 to 0.86; p<0.001). The number needed to treat to prevent one fall was three.[36]

Data about the effect of nutrition on bone health-related outcomes in people with osteoporosis or osteopenia are limited. The evidence identified in our SLR was insufficient to determine the effect of vitamin D analogues, non-soy protein or daily vitamin K on BMD or fractures in older women with T scores between −1 and ≥−2.5.[44–46] Nonetheless, maintenance of a healthy weight, increased consumption of fresh fruit and vegetables, lowering sodium intake and ensuring country-specific recommended intake levels of dietary calcium, may favourably impact bone health.[47] Adequate serum levels of vitamin D are important for good musculoskeletal health, although the effect of supplementation on bone health-related outcomes remains contested.[48–50] Analysis of pooled data from RCTs showed vitamin D supplementation had no effect on falls (n=34 144, relative risk (RR) 0.97, 95% CI 0.93 to 1.02) or total fractures (n=44 790, RR 1.00, 95% CI 0.93 to 1.07).[51]

The effect of face-to-face patient education on bone health-related outcomes in people with bone fragility is uncertain.[52] In a systematic review including 13 RCTs of mostly high or moderate risk of bias, outcomes, including knowledge about osteoporosis, initiation and adherence to osteoporosis medication and fractures, were mixed;[52] less than half of the studies reported a statistically significant difference favouring the intervention.

Despite insufficient evidence to determine the effect of some interventions, the task force agreed that non-physician HPs should offer multicomponent interventions including nutrition, multifactorial fall prevention initiatives and education, along with exercise (in particular supervised progressive weight-bearing, strength and balance training), to patients at high-risk of falls and or primary fragility fracture.

Point to consider 4: avoidance of smoking and overuse of alcohol

The negative impact of tobacco smoking on bone and bone-health related outcomes are widely recognised.[53] Smoking adversely affects bone mass in some populations,[54 55] and results from meta-analyses consistently demonstrate increased risk of osteoporotic fractures in people who currently smoke compared with never or non-smokers.[56–59]

High intakes of alcohol (more than two units/day or ≥50 g/day) also increase fracture risk.[60 61] The effects of alcohol on bone are complex and dose-dependent, and influenced by both direct and indirect mechanisms, such as alterations in activity and numbers of osteoblast and osteoclasts, hormonal changes and impaired nutrition.[62] For some, the consequences of skeletal fragility are exacerbated by increased risk of falling[63] mediated by intoxication and/or neuropathy.

Point to consider 5: exercise and nutritional interventions for patients who have experienced a fragility fracture

Following hip fracture surgery, structured exercise interventions, in particular interventions that incorporate progressive resistance exercise training, result in small but significant improvements in mobility and physical function.[64 65] Multicomponent exercise, incorporating strength and balance training, reduces risk of falls in people who have experienced an osteoporotic fracture,[40] while regular long-term resistance and weight-bearing exercise may favourably affect BMD.[41] Evidence about the optimal frequency, intensity and duration of exercise for people with osteoporotic fracture is limited. However, several country-specific recommendations drawing on expert consensus, in combination with evidence, are available to guide practice.[66 67]

Concerning the effect of nutrition on bone health, insufficient evidence was found to determine the effect of oral protein supplementation on functional outcomes in people following hip fracture[68] while vitamin D (800 IU) and calcium (1000 mg) supplementation in older people with a history of osteoporotic fracture appeared generally ineffective in preventing future hip or any new fracture.[69] One RCT, at low risk of bias, investigated the effect of a single loading dose of vitamin D3 compared with a placebo injection administered to older people within 7 days of hip fracture surgery.[70] At 4 weeks there was no statistically significant between-group difference in fracture incidence, but the falls rate of participants in the active group was 250 (number of falls/days x 1000) compared with 821.4 in the placebo group (absolute risk reduction 57.1%).

The task force considered these findings and agreed that non-physician HPs should encourage adequate nutrition for patients with a history of osteoporotic fracture and discuss vitamin D and calcium intake with them, focussing on actual and recommended

daily calcium intake, calcium and vitamin D rich foods and the individual's risk/benefit profile for vitamin D supplementation.

Point to consider 6: organisation and coordination of multidisciplinary services

The clinical and cost-effectiveness of coordinated multidisciplinary post-fracture models of care was confirmed in our SLR.[71–73] Orthogeriatric services, delivering collaborative multidisciplinary inpatient care to older people admitted with hip fracture, reduce relative risk of in-hospital and long-term mortality compared with standard care. Functional recovery and factors associated with risk of falling may also be positively impacted by early multidisciplinary HP team care approaches.[74 75]

Alongside, multidisciplinary fracture liaison services (FLS), in which non-physician HPs such as nurses, pharmacists and physiotherapists effectively coordinate case finding, risk stratification and secondary fracture prevention,[76] reduce re-fracture rates. In a meta-analysis of 19 519 participants who had experienced an osteoporotic fracture, a FLS compared with no FLS or usual care reduced absolute risk of re-fracture rate by approximately 30%.[72] Irrespective of the care model or country, FLS when compared with usual care or no treatment are cost-effective.[73]

Many countries in Europe have now implemented coordinated post-fracture multidisciplinary models of care based on best practice standards,[77] and the task force recommended that non-physician HPs should be included in these services.

Point to consider 7: adherence to anti-osteoporosis medicines

Despite the efficacy of anti-fracture pharmaceuticals,[78 79] rates of non-adherence to anti-osteoporosis medicines are high[80 81] and adversely affect outcomes.[82] Non-adherence to medicines can be characterised by non-initiation of a prescription, suboptimal implementation and premature discontinuation of treatment.[83] Interventions to improve adherence commonly target drug regimens, systems, providers and patients, although effects are inconsistent in people with chronic health problems.[84] There is some evidence that interventions delivered by HPs (education, less frequent dosing regimens, electronic prescription and pharmacist-delivered osteoporosis management services) may improve adherence to anti-osteoporosis medications.[85–87] Consequently, the task force agreed that non-physician HPs should evaluate medication adherence in patients prescribed anti-osteoporosis medicines, and explore ways to improve adherence.

Research and education agenda

The research and education agendas (boxes 1 and 2), support the development of capability and capacity within the non-physician workforce to prevent and optimally manage fragility fractures in adults 50 years or older. We recommend that consensus-derived core competencies are identified and embedded in HP education and training.

DISCUSSION

These EULAR points to consider, underpinned by shared decision-making and multi-professional working complement the previous EULAR/EFORT recommendations.[8] They provide a template for the organisation and delivery of healthcare by non-physician HPs to prevent and manage fragility fractures and contribute to holistic patient management.[88] In addition to fall risk evaluation and interventions delivered by non-physician HPs, the task force developed a separate point to consider, focussed on adherence to medicines. While some non-physician HPs prescribe medicines, all non-physician HPs should address, monitor and support adherence to prescribed anti-osteoporosis medicines in patients at risk of fragility fracture.

We acknowledge that patient management and HP roles and responsibilities differ across countries. However, these points can be tailored and used jointly by stakeholders as a focus for contextualised formative evaluations about implementation of interventions delivered by non-physician HPs, underpinned by country-specific patient level data from audit databases and registries.[89–91] The generation of this knowledge, in conjunction with the identification of contextual barriers and facilitators to optimal management and implementation strategies,[92 93] could enhance the role and impact of non-physician

Box 1 Research agenda to prevent and optimally manage fragility fractures for non-physician health professionals (HPs) including (but not limited to) dietitians, nurses, occupational therapists, pharmacists and physiotherapists

- Randomised clinical trials on the effect of non-pharmacological interventions, as well as interventions to facilitate adherence.
- Research studies need to define and qualify those at high-risk of fragility fracture in patient sample populations.
- Research studies investigating interventions to prevent falls and fragility fractures need to clearly record fracture status at baseline.
- Validation and reliability testing of (multicomponent) screening methods for risk of falling is needed.
- Research studies need to include long-term follow-up measures of bone health, incidence rates of falls and fractures and functional mobility outcomes.
- A consensus agreement and statement between relevant stakeholders on the definition of high-risk of secondary fracture is required.
- Further clinical trials to evaluate the cost-effectiveness of management of patients with osteoporosis and/or a (high-risk) of fragility fractures by non-physician HPs are needed.
- Research studies to identify the clinically effective optimal duration, intensity and frequency of interventions delivered by non-physician HPs to patients following fragility fracture should be conducted.

Box 2 Non-physician health professional (HP) education agenda to prevent and optimally manage fragility fractures

Non-physician HPs should be educated on:

- How to use (multicomponent) screening tools to understand fracture risk.
- How to deliver, and what to include in a falls prevention programme.
- How to tailor education for people and patients with varying risk of falls.
- The scope and role of non-physician HPs in fracture liaison services.
- How to support and promote medication adherence.
- How to effectively promote bone health.
- Medication side effects that impact on bone health.

Education standards need to be agreed and underpinned by learning principles.

HPs working alongside medical colleagues to deliver services for this patient population.

We recommend that education about osteoporosis, fall and fracture risk assessment, and interventions to prevent and optimally manage fragility fractures, should be a core component of non-physician HP undergraduate training. An interdisciplinary focus through generic competencies for non-physician HPs in fragility fracture prevention and management, may lead to more consistent and effective care, and tackle the personal, societal and economic burden associated with fracture events.

The low levels of evidence for some points to consider call for well-designed research studies that include specific non-physician HP interventions. Such studies should consider using behavioural change techniques to enhance adherence to interventions delivered by non-physician HPs and optimise service delivery to prevent and manage fragility fractures.

Our study has some limitations. First, over half of our points to consider were formulated wholly or in part based on the expert opinion of the task force, due to insufficient published research evidence. Our definition of high-risk populations probably excluded evidence from other studies examining commonly used interventions, such as multifactorial falls prevention strategies for other older adult populations. Second, our SLR preferentially selected systematic reviews and large RCTs and may have excluded some studies. Third, while data extraction and risk of bias judgements were conducted systematically, duplicate independent assessments would have added further value. Lastly, the addition of a general practitioner on the task force would have been beneficial.

CONCLUSION

The personal, societal and economic burdens associated with fragility fractures are enormous. These EULAR points to consider, based on robust development processes and agreed by an international task force, can guide non-physician HPs in the prevention and management of fragility fractures in adults 50 years or older.

Author affiliations
[1]School of Health Sciences, University of Southampton, Southampton, UK
[2]Department Care I, Musculoskeletal System & Neurology, Dutch National Health Care Institute, Diemen, The Netherlands
[3]EULAR Standing Committee of People with Arthritis/Rheumatism in Europe (PARE), Zurich, Switzerland
[4]EULAR Young PARE, Zurich, Switzerland
[5]Slovak League Against Rheumatism, Piestany, Slovakia
[6]Medicine for Older People, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[7]Department of Rheumatology, Aarhus University Hospital, Arrhus, Denmark
[8]INSERM U1153, Paris Descartes University, Reference Center for Genetic Bone Diseases - Department of Rheumatology, Cochin Hospital, Paris, France
[9]Department of Orthopedics and Trauma-Surgery, Medical University of Vienna, Vienna, Austria
[10]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK
[11]Rehabilitation, Physical Medicine and Rheumatology, 'Victor Babes' University of Medicine and Pharmacy, Timisoara, Timisoara, Romania
[12]Section for Outcomes Research, Centre for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna, Austria
[13]Department of Rheumatology, VU University Medical Centre Amsterdam, Amsterdam, Noord-Holland, The Netherlands
[14]Centre for Biomedical Research, Department of Biomedical Sciences and Medicine, University of Algarve, Faro, Portugal
[15]Department of Balneology, Rehabilitation and Rheumatology, 'Victor Babes' University of Medicine and Pharmacy, Timisoara, Timisoara, Romania
[16]Internal Medicine 3, Division of Rheumatology, Medical University Vienna, Vienna, Austria
[17]Trauma & Orthopaedics, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[18]Day Hospital, Alicante General and university Hospital, Alicante, Spain
[19]Ludwig Boltzmann Institute Arthritis and Rehabilitation, Vienna, Austria

Twitter Paul Studenic @Stiddyo and Jenny de la Torre-Aboki @JennydelaTorr16

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ORCID iDs
Jo Adams http://orcid.org/0000-0003-1765-7060
Nicky Wilson http://orcid.org/0000-0001-7404-7360
Karine Briot http://orcid.org/0000-0002-6238-2601
Paul Studenic http://orcid.org/0000-0002-8895-6941
Jenny de la Torre-Aboki http://orcid.org/0000-0002-4905-2034
Tanja A Stamm http://orcid.org/0000-0003-3073-7284

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2019 EULAR points to consider for the assessment of competences in rheumatology specialty training

Francisca Sivera ,[1,2] Alessia Alunno ,[3] Aurélie Najm ,[4,5] Tadej Avcin,[6] Xenofon Baraliakos ,[7,8] Johannes W Bijlsma,[9] Sara Badreh,[10] Gerd Burmester,[11] Nada Cikes,[12] Jose AP Da Silva ,[13,14] Nemanja Damjanov,[15] Maxime Dougados,[16] Jean Dudler,[17] Christopher J Edwards,[18] Annamaria Iagnocco,[19] Frédéric Lioté,[20,21] Elena Nikiphorou ,[22] Marloes van Onna,[23,24] Simon R Stones,[25] Dimitrios Vassilopoulos,[26] Catherine Haines,[27] Sofia Ramiro [28,29]

Handling editor Josef S Smolen

For numbered affiliations see end of article.

Correspondence to
Dr Francisca Sivera, Dpt Clinical Medicine, Miguel Hernandez University of Elche, 03550 Elche, Valenciana, Spain; fransimas@yahoo.es

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ABSTRACT

Background and aim Striving for harmonisation of specialty training and excellence of care in rheumatology, the European League Against Rheumatism (EULAR) established a task force to develop points to consider (PtCs) for the assessment of competences during rheumatology specialty training.

Methods A systematic literature review on the performance of methods for the assessment of competences in rheumatology specialty training was conducted. This was followed by focus groups in five selected countries to gather information on assessment practices and priorities. Combining the collected evidence with expert opinion, the PtCs were formulated by the multidisciplinary task force, including rheumatologists, medical educationalists, and people with rheumatic and musculoskeletal diseases. The level of agreement (LoA) for each PtC was anonymously voted online.

Results Four overarching principles and 10 PtCs were formulated. The overarching principles highlighted the importance of assessments being closely linked to the rheumatology training programme and protecting sufficient time and resources to ensure effective implementation. In the PtCs, two were related to overall assessment strategy (PtCs 1 and 5); three focused on formative assessment and portfolio (PtCs 2–4); three focused on the assessment of knowledge, skills or professionalism (PtCs 6–8); one focused on trainees at risk of failure (PtC 9); and one focused on training the trainers (PtC 10). The LoA (0–10) ranged from 8.75 to 9.9.

Conclusion These EULAR PtCs provide European guidance on assessment methods throughout rheumatology training programmes. These can be used to benchmark current practices and to develop future strategies, thereby fostering continuous improvement in rheumatology learning and, ultimately, in patient care.

INTRODUCTION

Rheumatology specialty training is the educational process required for a physician to formally become a specialist in rheumatology. It is defined by an officially approved training programme which aims to bring physicians to an agreed standard of proficiency regarding the management of people with rheumatic and musculoskeletal diseases (RMDs). The definition of the aims, structure and contents of each country's rheumatology training programme is under the exclusive domain of national authorities. However, the harmonisation of specialist training in Europe is deemed essential to ensure equity of access to high standards of care for all people with RMDs and to support the movement of rheumatology specialists across countries.[1] Available data on training programmes in Europe show a wide heterogeneity on their length, structure and content.[2 3]

For decades, educationalists have highlighted the relationship between learning and assessment.[4] Indeed, learning is often driven by assessment.[5] Assessment during training has apowerful impact on motivating learners on their path towards assessment for certification purposes. Regular and repeated testing can increase the retention of knowledge[6] and the skill performance[7] in undergraduate medical students. Even though evidence is scarce, the same paradigm is thought to apply to other types of assessment within higher education, such as specialty medical training.

The aim of this task force was to develop European League Against Rheumatism (EULAR) points to consider (PtCs) for the assessment of competences during rheumatology specialty training with the broader goals of enhancing learning during rheumatology specialty training, contributing to the harmonisation of training outcomes across Europe and improving the care provided to people with RMDs.

METHODS

After approval by the EULAR Executive Committee, the convenor (FS) and the methodologists (CH and SR) led a multidisciplinary task force guided by the 2014 updated EULAR standardised operating procedures.[8] The task force consisted of 23 members, including rheumatologists with an interest in medical education (two of them also representing the Emerging Eular Network), a methodologist, a medical educationalist, and two people with RMDs, from 12 different countries. Two face-to-face meetings of the task force were held in November 2018 and October 2019. Two fellows (AA and AN), guided by the methodologists, performed a systematic literature review (SLR), retrieving individual studies on methods of assessment in rheumatology specialty training and SLRs of studies from other

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Table 1 Glossary of terms related to the assessment of competences

Term	Definition
Assessment	A systematic process of gathering and analysing information on competences in order to measure a learner's achievement
CanMEDS framework	The most widely accepted and applied physician competency framework in the world, using a framework to explicit the knowledge, skills and behaviours associated with specific competences across seven roles: medical expert, professional, communicator, health advocate, collaborator, scholar and leader
Competence	An observable ability of a physician related to a specific ability that integrates knowledge, skills and behaviours and that develops through the stages of expertise from novice to master clinician
Curriculum	The description of the outcomes required, and the activities and experience prescribed to develop and demonstrate those outcomes
Direct observation of procedural skills (DOPS)	A workplace-based assessment to evaluate the competence in performing a required technical skill.
Feedback	A process whereby an individual is given information about their performance in order to help them learn and progress
Formative assessment	Information about a learner's performance or understanding, which is provided to the learner as part of the learning process so that they are stimulated to improve their performance and progress towards the required level of competence
Mini clinical examination (mini-CEX)	A workplace-based assessment to evaluate how effectively a clinician interacts with a patient
Multisource feedback	A system that collects the anonymous appraisal of the trainee's performance in an everyday clinical setting, by a variety of coworkers, from mentors to colleagues, nurses and patients; this tool is especially valuable to address issues related to professionalism
Objective structured clinical evaluation (OSCE)	A carefully designed examination circuit of different time-limited stations, each dedicated to the assessment of performance at a particular simulated task
Portfolio	A repository for multiple formative assessments, reflections and records of achievements
Professionalism	A set of values, behaviours and relationships that underpins the trust that the public has in doctors; as professionals, physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation and maintenance of personal health
Summative assessment	A measure of a learner's performance or understanding which sums up and grades whether the learner has succeeded in reaching the required level of competence

related medical specialties.[9] As published evidence on assessment methods was limited, a qualitative study using focus groups in five European countries (Denmark, Netherlands, Slovenia, Spain and UK) gathered insights into current practices and priorities.[10] These countries were selected to provide a representation of different assessment structures and cultures. The SLR and qualitative study are published separately; however, they form an integral part of the project.

Based on the presented evidence and expert opinion, and following a process of iterative discussion, the overarching principles and PtCs were developed across two 1-day task force meetings. For every statement, formulations were presented, discussed and voted on (informal voting). The statements were accepted if at least 75% of the task force approved the wording in the first round. If this was not reached, further discussion ensued and wording was refined. At least a 67% approval rate was required in the second voting round. If a third voting round was necessary, a simple majority was sufficient. Prompted by discussions during the meetings, the task force felt the need to develop a glossary (table 1) in order to standardise terminology.

After the meeting and once the PtCs were finalised, the level of evidence supporting each statement and the grade of recommendation was assigned following the Oxford Centre for Evidence-Based Medicine procedures.[11] Finally, each task force member anonymously indicated their level of agreement (LoA) with each PtC online (numerical rating scale ranging from 0='do not agree at all' to 10='fully agree'). In addition, based on the limited nature of the available evidence and the issues raised among the task force, a research agenda was formulated.

The final manuscript was reviewed and approved by all task force members, followed by ratification by the EULAR Executive Committee and the Rheumatology Section and Board of the European Union of Medical Specialists (UEMS).

RESULTS

Four overarching principles and 10 PtCs were formulated (table 2). Overall, the evidence underpinning these PtCs in the rheumatology setting is scarce, so the emphasis was placed on general expertise and consensus.

Overarching principles

Rheumatology training should generate rheumatologists capable of and committed to delivering the best care to people with RMDs

During rheumatology training, the physician should acquire the knowledge, skills and professional behaviours necessary to ensure delivery of optimal care to people with all types of RMDs throughout their careers.

Assessment of competences is vital to guide learning and to guarantee quality of care

In the past decades, there has been a move towards 'assessment for learning', in which the assessment environment encourages trainees to feel responsible for driving and appraising their own learning.[12]

Assessment is an integral part of training and must be guided by and aligned with a clear set of educational objectives established by the curriculum

The task force agreed on the need for assessments to be embedded into a structured strategy conveyed by the overall training programme. The curriculum provides the framework of learning objectives, each corresponding to adequate methods of teaching, learning and assessment. National curricula are available in most countries. Additionally, the UEMS Rheumatology Section and Board provides a European curriculum.[13]

Effective assessment requires protected time and resources

One of the key barriers to adequate assessment, identified by trainees and trainers alike throughout Europe, is the lack of protected time for this purpose.[10] In order to improve the clinical learning environment, it is essential that educational supervisors, programme directors and national authorities recognise this need and identify and provide the necessary resources.[14]

Table 2 Overarching principles and points to consider for the assessment of competences in rheumatology specialty training, with LoA and for the specific points, levels of evidence

Overarching principles	LoA, mean (SD)	
1. Rheumatology training should generate rheumatologists capable and committed to deliver the best of care to people with rheumatic and musculoskeletal diseases.	9.9 (0.45), 100%≥8	
2. Assessment as an integral part of training must be guided by and aligned with a clear set of educational objectives established by an official/national/accepted curriculum.	9.8 (0.52), 100%≥8	
3. Assessment of competences is vital to guide learning and to guarantee quality of care.	9.8 (0.41), 100%≥8	
4. Effective assessment requires protected time and resources.	9.7 (0.73), 95%≥8	
Points to consider	**LoE**	**LoA, mean (SD)**
1. Assessment of competences should be a structured and continuous process regularly carried out throughout the training period.	5	9.75 (0.55), 100%≥8
2. Formative assessment with constructive feedback should be frequently performed and with a greater frequency than summative assessment.	5	9.4 (0.82), 100%≥8
3. Feedback should aim to stimulate reflections by the trainee on how to achieve standards of competence and professional behaviour.	5	9.65 (0.67), 100%≥8
4. Trainees should maintain an updated portfolio, including feedback and evidence of self-reflection, to be used as part of the assessment process.	5	9.4 (0.75), 100%≥8
5. Different methods of assessment should be carried out throughout training as multiple methods of assessment can provide a complete overview of a trainee's competence.	5	9.75 (0.64), 100%≥8
6. Multiple-choice case-based questions should be the preferred form of knowledge assessment.	5	8.75 (1.83), 75%≥8
7. Clinical skills should be assessed either in the workplace (direct observation of procedural skills or the mini-clinical examination exercise) and/or in a simulated context (observational structured clinical examination)	5	9.35 (0.81), 100%≥8
8. Competences related to professionalism should be formally assessed using multisource feedback/360° method.	5	9.25 (0.97), 95%≥8
9. The training programme should incorporate predefined processes to identify and support trainees at risk of failure.	5	9.6 (0.75), 100%≥8
10. Trainers should receive continuous training in assessment methods and strategies, particularly in providing constructive feedback.	5	9.4 (1.23), 95%≥8

Numbers in the column 'LoA' indicate the mean (SD) of the LoA and the percentage of task force members with an LoA of at least 8 (0–10). LoE: based on the Oxford Centre for Evidence-Based Medicine classification, with 'level 1' corresponding to meta-analysis or RCTs or high-quality RCTs; 'level 2' corresponding to lesser quality RCTs or prospective comparative studies; 'level 3' corresponding to case–control studies or retrospective studies; 'level 4' corresponding to case series without the use of comparison or control groups; and 'level 5' corresponding to case reports or expert opinion.[11]
LoA, level of agreement; LoE, level of evidence; RCT, randomised controlled trial.

Points to consider

Assessment of competences should be a structured and continuous process, regularly carried out throughout the training period

Assessments should not be performed at a unique time point (eg, final examination); rather, they should be spaced out throughout the training, allowing the trainee to identify areas for improvement before a final summative assessment. Providing a specific recommendation on minimum or optimal assessment frequency was discussed in depth by the task force; however, it was thought that this needed to be flexible enough to be applied in different national contexts. Frequency should be enough to provide adequate feedback and to guide learning throughout the training programme. Some types of assessment, such as the identification of unprofessional behaviours with appropriate feedback, should take place continuously.

Formative assessment with constructive feedback should be regularly performed and with a greater frequency than summative assessment

Assessments can be performed with a formative or a summative aim. Summative assessment assigns grades to trainee performance at designated points in the curriculum, allowing comparison with established standards or between trainees, and a pass/fail decision. For example, an examination at the end of medical training, on which the decision to qualify for medical practice hinges, is a summative assessment. On the other hand, formative assessment is designed as an ongoing part of the instructional process to support and enhance learning and reflection. Formative assessment aims to stimulate the trainee to identify areas for improvement and to provide a plan to that purpose. Frequent, high-quality discussions about current performance, together with expert and customised suggestions for improvement, are associated with more effective learning and higher satisfaction in trainees.[15]

Feedback should stimulate reflection by the trainee on how to achieve the standards of competence and professional behaviour

Feedback is a core component of effective assessment, informing trainees of their progress (or lack of), observed learning needs (and available resources to facilitate learning) and providing motivation to undertake appropriate learning activities.[16] Feedback has the potential to change physicians' behaviour in different environments,[17] including clinical performance and professional conduct. Feedback should prompt self-reflection and management of the weaker aspects of performance. In the focus groups, both trainees and trainers identified feedback as a priority.[10]

Trainees should maintain an updated portfolio, including feedback and evidence of self-reflection, to be used as part of the assessment process

Portfolios are instruments used to collect and assess evidence of a trainee's experience and progression in tasks and competences.[18] They provide a key connection between learning at individual and organisational levels. The implementation of portfolios throughout Europe varies, and there is no consensus on their aims, design and content. The task force felt that portfolios should extend beyond a 'logbook' list of patients managed, procedures performed, courses attended or research performed. Rather, they should be an integral part of the continuous formative process and self-learning; as such, they should include examples of assessors' feedback and trainees' self-reflection. In order to promote honesty and self-critique, reflections included in the portfolio should be kept private and should not be misused or misconstrued in legal contexts. Use of electronic portfolios and, even better, integration within e-learning platforms increase their utility and address one of the key complaints of trainees[10]—the excessive time spent in their compilation. The EULAR portfolio task force has developed a portfolio structure which can be considered for uptake in different countries.[19]

Different methods of assessments should be carried out throughout training, as no single method of assessment can provide a complete overview of trainee competences

During training, rheumatologists acquire a wide variety of competences ranging from the ability to independently manage people with different forms of RMDs to the performance of specific skills (eg, aspirating a knee joint) or the acquisition of professional attitudes (eg, commitment to lifelong learning). No

single method of assessment can properly evaluate all competences. For example, written exams are unable to assess how a trainee works within a multidisciplinary team or whether they can perform a joint injection. In fact, the correlation between scores from assessment tools evaluating different competences is very weak.[20–24] On the other hand, different assessment methods can be used to assess a single competence, providing complementary information. For instance, the ability to aspirate a joint can be assessed with a mannequin (simulation) or on a real person with an RMD (eg, workplace-based via direct observation of procedural skills (DOPS)). In the second instance, assessment of a trainee's skill in patient communication or respect for patient autonomy can be included. When implementing a training programme and designing a local assessment strategy, thought must be given as to how each competence is assessed.

Multiple-choice case-based questions should be the preferred form of knowledge assessment

Each competence is composed of the integration of specific knowledge, skills and professional behaviours.[25] When assessing knowledge, we are therefore not assessing overall competence, but one of the core pillars that support it. Emphasis was placed on the fact that multiple choice questions (MCQs) should be based on a clinical scenario (case-based), allowing the assessment of complex clinical reasoning rather than the mere memorisation of specific facts. Oral examinations, commonly known as *vivas*, are not recommended as the inclusion of few examiners, the sampling of limited content and the use of a global judgement result in poor reliability.[26]

Clinical skills should be assessed in the workplace (DOPS) or the mini-clinical examination exercise (mini-CEX) and/or in a simulated context (observational structured clinical examination (OSCEs))

Clinical skills and competences can be assessed in a simulated environment or directly in the workplace. In simulated environments, the recommended assessment tool is the OSCE. An OSCE consists of multiple, time-limited stations where trainees perform specific tasks, under structured assessment. At each station, trainees are marked against standardised scoring checklists by trained assessors. In this manner, an OSCE can assess many competences. Typical competences assessed in this manner include performing a site-specific clinical examination, discussing treatment options or skills such as the identification of crystals in a synovial fluid sample.[20 21] Patient experts can be trained to role-play a patient with a given disease. In workplace assessments, a trainer observes the trainee interacting with a patient around a clinical task (mini-CEX) or a procedure (DOPS). The trainer uses a structured form to assess and provide feedback to the trainee. Encounters can take place in a variety of settings (inpatient, outpatient, emergency room) and contexts (initial or follow-up visit). The mini-CEX can be used to assess competences such as taking a focused history or performing a physical examination, while the DOPS is tailored for procedures such as joint aspiration, crystal identification or joint ultrasonography. Overall, each patient encounter takes 15–30 min followed by 5–10 min of feedback. It is expected that trainees are assessed several times throughout the year of training, with different trainers and in different clinical situations or with different focuses, so that different competencies are assessed.[5] A similar case may be especially dedicated to assess clinical examination or management planning, for example. The EULAR portfolio task force is developing forms for both the mini-CEX and the DOPS.[19]

Competences related to professionalism should be formally assessed using multisource feedback (MSF)/360° method

Professionalism is key to a good clinical practice and should be part of training and assessment. However, the assessment of professionalism is hampered by varying definitions and the difficulty in transforming the elements of professionalism into aspects that can be taught and measured.[27] It is beyond the scope of these PtCs to establish which aspects of professionalism should be assessed; these could include areas such as ethical practice, effective interaction with patients and relatives, working effectively with other health professionals, health authorities and other stakeholders, reliability and commitment to continuous improvement.[28] The MSF, also known as the 360° evaluation, allows the systematic collection of data on a trainee's performance, acquired anonymously from a variety of coworkers. Typically, 10–20 assessors comment on a specified range of that person's functioning. The assessors may include trainers, physicians, trainees, nurses, medical students, health professionals, patients and administrative personnel. MSF is especially useful in assessing actual behaviours in the workplace which are difficult to measure, or which can be concealed under formal assessment conditions. The results from the MSF should be discussed with the trainee in order to promote reflection.

The training programme should incorporate a predefined process to identify and support trainees at risk of failure

The identification of trainees who are at risk of failure within training programmes is a challenge.[29] Some trainers feel unprepared and/or unwilling to report a trainee's underperformance. Barriers include lack of documentation, lack of knowledge of what to document, anticipation of an appeal process and lack of remediation options.[30] Assessor development programmes, a strong assessment system with clear standards to be achieved at different training levels and a support system that offers guidance to the failing trainee are deemed essential.[31]

Trainers should receive regular training in assessment methods and strategies, particularly in providing constructive feedback

The existence, depth and scope of development programmes in assessment methods vary widely among countries[10] and can even be training centre-specific. Accepted training and assessment methods evolve with time as new evidence accrues. Continuous professional development in assessment methods and strategies should be encouraged by relevant stakeholders. Of special importance is training in providing constructive feedback,[32] a far more complex competence than it may seem. There is a recognised gap between the feedback given and what is perceived by the trainee. Feedback is effective when it leads to an improvement in the performance of the trainee. Both the skills of the person selecting and providing the feedback and the willingness and ability of the recipient to engage with it can modulate its effectiveness.

DISCUSSION

These are the first EULAR-endorsed PtCs for the assessment of competences in rheumatology specialty training. Their aim is to serve as a benchmark and an inspiration toinvolved stakeholders. In total, 41 EULAR countries provide rheumatology specialty training. Each country has its own training structure, curriculum and assessment strategy, resulting in a wide heterogeneity.[2] Some countries provide a comprehensive list of assessments to be undertaken, while some provide national, summative final examinations, and others provide broad statements. Overall,

Box 1 Research agenda

Barriers and enablers
- What are the key features of an assessment strategy that impact the professional development of trainees in a rheumatology training programme?

Competency components
- Which competences should be subjected, as a minimum, to formative assessment during the specialty training programme?

Frequency
- How often should formative (and summative) assessments take place?
- How often should each assessment method (eg, mini-CEX and DOPS) be performed?

Impact, value and outcomes
- How does a structured assessment of competences throughout training impact on training/learning outcomes and on care delivery outcomes?
- What is the impact of the use of a proper portfolio on training/learning outcomes and on care delivery outcomes?
- What is the added value of a summative assessment in the presence of a structured formative assessment programme?
- Do improvements in the quality of assessments translate into better outcomes and satisfaction for trainees and especially for patients?

Validity and reliability
- What is the validity of mini-CEX, DOPS and MSF in a rheumatology setting?
- What are the minimum requirements for an OSCE to be valid and reliable in a rheumatology training programme?

DOPS, direct observation of procedural skills; mini-CEX, mini clinical examination; MSF: multisource feedback; OSCE, objective structured clinical evaluation.

the specific implementation remains largely dependent on each centre's culture and attitude. These PtCs in no way attempt to undermine local regulations. Rather, they seek to provide recommendations of good practice, which can help stakeholders analyse their own assessment strategy and inspire positive change, where appropriate.

Many practising physicians are involved in assessing the competences of trainees. However, some are not as comfortable using educational assessment tools as they are managing patients with RMDs.[33] Assessment tools can measure knowledge or demonstrate competence in a simulated or in a 'real-life' setting.[34] Written examinations with MCQs can assess pure knowledge, but they are best employed in assessing its application to clinical problems; for this purpose, context-specific questions, based on a clinical scenario should be used. OSCEs can evaluate a trainee's skills and competences in a simulated environment. OSCEs can be used for both common or rarer diseases, highlighting the need for systematic assessment that might provide clues for the differential diagnosis, while rare diseases might be difficult to evaluate in workplace-based assessments. However, in order to evaluate what a trainee actually does, assessment needs to take place within the workplace by direct observation of a trainee's performance in a 'real-life' setting. Implementing a structure and effective assessment strategy within a busy clinic is a challenge, highlighting one of the barriers to workplace assessment. Tools such as the mini-CEX or the DOPS facilitate the standardisation of the assessment and feedback of clinical encounters and procedures. Professionalism is key to becoming an effective physician but is one of the most difficult aspects to define and measure. While some aspects of professionalism can be assessed in a simulated context (eg, efficient patient communication in an OSCE), most should be explored in the workplace. The major barrier for effective implementation of this multimodal assessment strategy is lack of time and resources (eg, trained trainers). Support from training centres, institutions and national authorities is key.

Even though specific evidence from rheumatology studies supporting these PtCs was scarce, the LoA with the PtC was very good. Published evidence identified in the SLR[9] was limited to the evaluation of some aspects of validity or reliability of a few assessment tools (OSCE, mini-CEX and DOPS). Indirect evidence, stemming from other medical specialties, provides additional support, but its applicability is varied, given the different contexts. As per EULAR standard operation procedures, the Oxford Levels of Evidence have been applied.[11] In medical education, quantitative evidence is scarce; specifically, evidence assessing the impact of different tools or strategies is lacking. Research allowing rheumatologists to implement best practices supported by consistent evidence would be welcome and is the basis of the proposed research agenda (box 1). While we await this, the high level of consensus that these recommendations provided is reassuring as to its cross-national validity.

In conclusion, these EULAR PtCs provide European guidance on assessment tools and strategies to be used throughout rheumatology training programmes. Given the relationship between learning and assessment, the harmonisation of assessment strategies could impact rheumatology training, encouraging stakeholders to strive for excellence and thereby optimise the future care delivered to people with RMDs.

Author affiliations
[1]Department of Clinical Medicine, Miguel Hernandez University of Elche, Elche, Spain
[2]Department of Rheumatology, Hospital General Universitario Elda, Elda, Spain
[3]Department of Medicine, Rheumatology Unit, University of Perugia, Perugia, Italy
[4]INSERM UMR1238, University of Medicine, CHU Nantes, Nantes, France
[5]Institute of Infection, Immunity and Inflammation, University of Glasgow College of Medical Veterinary and Life Sciences, Glasgow, UK
[6]Department of Allergology, Rheumatology and Clinical Immunology, University Children's Hospital Ljubljana, Ljubljana, Slovenia
[7]Rheumazentrum Ruhrgebiet, Herne, Germany
[8]Ruhr University Bochum, Bochum, Nordrhein-Westfalen, Germany
[9]Department of Rheumatology and Clinical Immunology, UMCUtrecht, Utrecht, Netherlands
[10]EULAR Patient Research Partner, Stockholm, Sweden
[11]Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, Germany
[12]Division of Clinical Immunology and Rheumatology, University Hospital Centre Zagreb, Zagreb, Croatia
[13]Reumatologia, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
[14]Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal
[15]Institute of Rheumatology, University of Belgrade School of Medicine, Belgrade, Serbia
[16]Rheumatologie B, Hopital Cochin, Paris, Île-de-France, France
[17]Service de Rhumatologie, HFR Fribourg, Hôpital Cantonal, Fribourg, Switzerland
[18]Musculoskeletal Research Unit, NIHR Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[19]Academic Rheumatology Center, Università degli Studi di Torino, Torino, Italy
[20]Department of Rhumatologie, Hôpital Lariboisière, Paris, France
[21]INSERM UMR-1132, University of Paris, Paris, France
[22]Centre for Rheumatic Diseases, King's College London, London, UK
[23]Department of Medicine, Division of Rheumatology, Maastricht University Medical Center, Maastricht, The Netherlands

[24]School for Public Health and Primary Care (CAPHRI), Maastricht University, Maastricht, The Netherlands
[25]EULAR Patient Research Partner, Manchester, UK
[26]2nd Department of Medicine and Laboratory, Clinical Immunology-Rheumatology Unit, Athens University School of Medicine, Athens, Greece
[27]Center for Teaching and Learning, University of Oxford, Oxford, UK
[28]Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[29]Rheumatology, Zuyderland Medical Center, Heerlen, The Netherlands

Twitter Francisca Sivera @FranciscaSivera and Elena Nikiphorou @ElenaNikiUK

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ORCID iDs
Francisca Sivera http://orcid.org/0000-0002-3414-1667
Alessia Alunno http://orcid.org/0000-0003-1105-5640
Aurélie Najm http://orcid.org/0000-0002-6008-503X
Xenofon Baraliakos http://orcid.org/0000-0002-9475-9362
Jose AP Da Silva http://orcid.org/0000-0002-2782-6780
Elena Nikiphorou http://orcid.org/0000-0001-6847-3726
Sofia Ramiro http://orcid.org/0000-0002-8899-9087

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Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement

Peter Nash ,[1] Andreas Kerschbaumer ,[2] Thomas Dörner ,[3] Maxime Dougados,[4] Roy M Fleischmann ,[5] Klaus Geissler,[6] Iain McInnes,[7] Janet E Pope ,[8] Désirée van der Heijde ,[9] Michaela Stoffer-Marx,[10] Tsutomu Takeuchi,[11] Michael Trauner,[12] Kevin L Winthrop ,[13] Maarten de Wit ,[14] Daniel Aletaha ,[2] Xenofon Baraliakos,[15] Wolf-Henning Boehncke,[16] Paul Emery ,[17] John D Isaacs,[18] Joel Kremer,[19] Eun Bong Lee ,[20] Walter P Maksymowych ,[21] Marieke Voshaar,[14] Lai-Shan Tam,[22] Yoshiya Tanaka ,[23] Filip van den Bosch,[24] René Westhovens ,[25] Ricardo Xavier,[26] Josef S Smolen [2]

Handling editor Dimitrios T Boumpas

For numbered affiliations see end of article.

Correspondence to
Professor Josef S Smolen, Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, 1090 Vienna, Austria; josef.smolen@meduniwien.ac.at and Professor Peter Nash, Griffith University School of Medicine, Herston, Gold Coast, QLD 9726, Australia; drpnash@tpg.com.au

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ABSTRACT

Objectives Janus kinase inhibitors (JAKi) have been approved for use in various immune-mediated inflammatory diseases. With five agents licensed, it was timely to summarise the current understanding of JAKi use based on a systematic literature review (SLR) on efficacy and safety.

Methods Existing data were evaluated by a steering committee and subsequently reviewed by a 29 person expert committee leading to the formulation of a consensus statement that may assist the clinicians, patients and other stakeholders once the decision is made to commence a JAKi. The committee included patients, rheumatologists, a gastroenterologist, a haematologist, a dermatologist, an infectious disease specialist and a health professional. The SLR informed the Task Force on controlled and open clinical trials, registry data, phase 4 trials and meta-analyses. In addition, approval of new compounds by, and warnings from regulators that were issued after the end of the SLR search date were taken into consideration.

Results The Task Force agreed on and developed four general principles and a total of 26 points for consideration which were grouped into six areas addressing indications, treatment dose and comedication, contraindications, pretreatment screening and risks, laboratory and clinical follow-up examinations, and adverse events. Levels of evidence and strengths of recommendations were determined based on the SLR and levels of agreement were voted on for every point, reaching a range between 8.8 and 9.9 on a 10-point scale.

Conclusion The consensus provides an assessment of evidence for efficacy and safety of an important therapeutic class with guidance on issues of practical management.

INTRODUCTION

The therapeutic options for patients with immune-mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis/ankylosing spondylitis (AxSpA/AS), systemic lupus erythematosus (SLE), psoriasis (PsO), atopic dermatitis (AD), Crohn's disease (CD), ulcerative colitis (UC) and others, have significantly improved over the past two decades. This results primarily from the introduction of several novel medications, in particular biological (b) disease-modifying antirheumatic drugs (DMARDs), as reflected in recent management recommendations.[1–6] Improved strategic utilisation of drugs has similarly impacted positively on outcomes.

Among all therapies developed for IMIDs over the last two decades, only tumor necrosis factor (TNF)-inhibitors exhibit a very broad efficacy across many diseases: RA, PsA, axSpA, juvenile idiopathic arthritis, PsO, CD, UC and uveitis.[7] Even though targeting just a single cytokine, no other treatment modality has yet been approved for such a broad list of indications, suggesting that TNF is pathogenetically involved across a diverse range of IMIDs. All other biological agents are licensed for fewer indications. This will likely change with the advent of Janus kinase (JAK)-inhibitors (JAKi), a new class of targeted synthetic DMARDs (tsDMARDs) that interfere with signal transduction pathways of a variety of cytokines and thereby have the potential to mediate immune modulatory benefits across a broad range of pathologies and their clinical phenotypes.

bDMARDs are usually monoclonal antibodies or receptor constructs that target a specific soluble or cell surface molecule, either a cytokine, a cytokine receptor or another cell membrane antigen. They either prevent interaction of the specific ligand with its cognate receptor, destroy a specific cell population, such as B-cells, or inhibit cross talk between particular cell populations. They have to be administered parenterally since they are proteins. They also do not enter the cell but mediate their respective modes of action outside the cell or via the cell surface.

The pathways that mediate cytokine receptor signal transduction have been elucidated in recent years providing novel and rational targets for drug development to modify cytokine effector function. Synthetic chemical agents that interfere with these pathways have been developed for various indications.[8–10] Among them, the JAKi represent a series of intracellularly active drugs, some of which have been approved for the treatment of several IMIDs. Five JAKi, tofacitinib, baricitinib, peficitinib, upadacitinib and filgotinib, are currently approved for therapeutic use in one or more IMIDs in a number of geographical regions.

Our experience with bDMARDs spans two decades across many diseases with thousands of patient years of experience including in registries in many countries. In contrast, data from registries are quite limited for JAKi and some have only recently been approved by several regulatory authorities; safety data for more than 10 years are derived mainly from long term extensions of randomised clinical trials.[11 12] Therefore, it was deemed important to develop an evidence-based consensus statement that focuses on practical issues in the use of JAKi.

Scope and purpose

Recommendations for the management of individual IMIDs focus primarily on therapeutic strategies and the general use of individual or groups of agents. While quite comprehensive, they usually address a particular disease and general issues, only rarely accommodating the various, often complex aspects related to the general application of an individual drug or a specific mode of action. Therefore, consensus statements on the more comprehensive use of specific agents or classes of drugs have also been developed.[13–16] These provide more detailed information on efficacy and safety of a class of drugs than in the traditional broad management recommendations. Such 'points to consider' can provide prescribers, like specialists in specific disease areas, and patients (especially when information is available for laypersons), with an expert opinion on appropriate use of a new drug and its place in treatment algorithms. When a drug is approved for more than one indication, a specific consensus statement can be used across specialties. Thus, the target of the present consensus statement comprises rheumatologists, dermatologists, gastroenterologists, other health professionals involved in these areas, patients with these respective diseases, but also hospital managers and representatives of regulators and social security agencies.

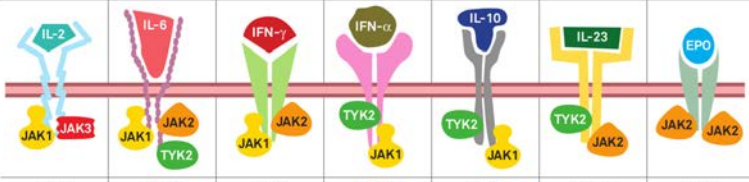
These points to consider are not meant to suggest a preferential use of JAKi for any particular disease but rather to provide evidence-based information in conjunction with expert opinion once an agent of this class has been considered for the treatment of a patient with a specific disease for which the drug is indicated. A research agenda will complement these points to drive momentum to search for more evidence where this is insufficient or lacking. Before addressing the methodology related to this document, we will briefly allude to the mode of action and other pharmacological aspects of this class of drugs.

Mode of action

JAKs are non-receptor tyrosine kinases associated with the cytoplasmic domain of type I and II cytokine receptors which are activated when these are engaged by their cognate ligands; once phosphorylated, they phosphorylate signal transducers and activators of transcription (STATs) which then induce gene activation.[17] JAKi reversibly inhibit kinase signalling for varying periods of the dosing cycle. They are oral small molecules that act intracellularly and prevent the phosphorylation of JAKs. Many cytokines, such as interleukin (IL)-2, 6, 12, 15 and 23 as well as interferons use the JAK-STAT pathways, while others, such as IL-1, IL-17 and TNF, do not (figure 1). In addition, haematopoietic growth factor receptors, such as those for erythropoietin (EPO), thrombopoietin and granulocyte-macrophage colony-stimulating factor, use the JAK-STAT pathway (figure 1). Within the cell usually different JAK molecules are associated with each of these receptor chains, acting in tandem as heterodimers, such as JAK1 and JAK2, JAK1 and JAK3 or JAK1 and TYK2. Only in the case of haematopoietic growth factor receptors both chains carry JAK2. Thus, JAK enzymes - JAK1, 2, 3 and TYK2 - function as dimers and once activated phosphorylate STATs, which subsequently induce gene transcription.

The selectivity of JAKs can be determined by using purified enzyme systems and a variety of cellular models.[18 19] Varying approaches may lead to differing results with respect to perceived selectivity of JAKs, and selectivity is dose-dependent, since at higher doses the compounds lose selectivity.[19 20] The in vivo selectivity may differ further so that in vivo markers may also be helpful. Reduction of inflammation usually produces an increase in haemoglobin, as exemplified by the rapid normalisation of anaemia in patients receiving monoclonal antibodies to the IL-6 receptor.[21] Since EPO signals through JAK2 homodimers, failing to see an increase in haemoglobin in patients with anaemia of chronic disease who experience clinical improvement on JAKi therapy suggests an important degree of JAK2 inhibition. Of note, failure to increase haemoglobin is not necessarily linked to fatigue and rarely a reason to stop a JAKi. Current views on the selectivity of JAKi, taking all aspects including clinical ones (such as effects on haemoglobin levels) into consideration are provided in figure 1. Of note, the totality of in vivo downstream effects of JAKi is still insufficiently understood, especially in specific disease settings, and an important matter for further research activities.

Given that individual JAKs and STATs can be activated by more than one cytokine, upregulation and activation of a single STAT pathway does not implicate any one particular cytokine in a response and as such our understanding of the hierarchical contribution of distinct STATs to effector pathways remains conjectural. Nevertheless, success and failure of therapeutic trials of drugs of known selectivity enable some insights into pathogenesis (figure 1). For example, both IL-6 and IL-23 receptors (R) signal via JAKs; since IL-6R inhibition does not appear efficacious in PsA or PsO, while IL-12 and IL-23 inhibition is,[22–24] this infers that beneficial effects of JAKi may arise by inhibiting IL-23 rather than IL-6 signalling. In contrast, IL-6R antibodies, but not anti-IL-12/23 antibodies,[25] are efficacious in RA and, therefore, JAKi may be assumed to convey efficacy by blocking IL-6 rather than IL-12 or 23 signal transduction. Moreover, neither IL-12, IL-23 nor IL-6R inhibition are efficacious in AS,[26 27] while JAKi appear to be[28]; consequently, this effect cannot be explained by interference with IL-6, IL-12 or IL-23 signal transduction, but rather by inhibition of signal transduction of other cytokines captured by JAKi (figure 1). However, also inhibition of type I (or type II) interferon signal transduction may play a role.[29 30] Similar deliberations may be made for inflammatory bowel disease, where IL-6R inhibition is not, or only weakly efficacious,[31] while IL-12/23 blockade is efficacious,[32] and for PsO.[33] On the other hand, while pan JAKi is apparently efficacious in UC but not in CD,[34 35] more JAK1 selective inhibitors (filgotinib, upadacitinib) showed promising results in CD,[36 37] implying that differences in the pathogeneses of these two inflammatory bowel diseases manifest in subtle but

Disease	Cytokines						
	IL-2	IL-6	IFNs		IL-10	IL-12 and IL-23	GM-CSF
PsA	ND	No	ND	ND	ND	Yes	ND
axSpA	ND	No	ND	ND	ND	No	ND
RA	No	Yes	ND	ND	ND	No	Yes
IBD	ND	No	ND	ND	ND	Yes	ND
PsO	ND	No	ND	ND	ND	Yes	ND
Cytokine and cytokine receptor families	Cytokine receptor sharing the γ-chain (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21)	Cytokine receptor sharing the gp130 (IL-6, IL-11, IL13, IL-25, IL-27, IL-31)	IFN-γ receptor	Type I IFN Receptor (IFN α/β)	IL-10 family receptor (IL-10, IL-22)	Receptors for Cytokine sharing the IL-12Rβ1 (IL-12,IL-23)	Homo-dimeric cytokine receptor (GM-CSF, EPO, TP, IL-3, IL-5)
							
	STAT 1, 3, 5, 6	STAT 1, 3, 5	STAT 1, 3, 5	STAT 1, 2, 3	STAT 1, 3, 5	STAT 3, 4	STAT 5

Drug	Selectivity*							
Baricitinib	JAK1, 2	+	+	+	+	+	+	+
Filgotinib	JAK1	+	+	+	+	+	-	-
Peficitinib	JAK1, 2, 3	+	+	+	+	+	+	+
Tofacitinib	JAK1, 2, 3	+	+	+	+	+	+	+
Upada-citinib	JAK1, (2)	+	+	+	+	+	+	+

*also taking the clinical perspective into account

Figure 1 Depiction of cytokines that activate and drugs that target Janus kinases (JAKs) presumably involved in the pathogenesis of immune-mediated inflammatory diseases (IMIDs). Top: efficacy of agents targeting specific JAK-inducing cytokines in different IMIDs. Centre: cytokines and respective receptors that trigger JAKs, types of JAKs activated and type of STATs (signal transducers and activators of transcription) activated by the respective JAKs. Bottom: JAK-inhibitors which are currently approved for IMIDs and their overall (including clinically derived) selectivity and presumed interference (+ or -) with certain cytokine pathways. axSpA, axial spondyloarthritis; EPO, erythropoietin; GM-CSF, granulocyte-monocyte colony stimulating factor; IBD, inflammatory bowel diseases; IFN, interferon; IL, interleukin; ND, not done; PsA, psoriatic arthritis; PsO, psoriasis; R, receptor; RA, rheumatoid arthritis; TP, thrombopoietin.[19 40 146 147]

functionally important variations in the relative contribution of these signalling pathways.[38] Finally while TNF does not activate the JAK-STAT pathway directly, it might do so indirectly via induction of other cytokines, such as IL-6 or type I interferons.[39] This adds further complexity to our understanding of the pathogenesis of IMIDs.

Thus, JAKi via its mode of action across signal transduction of multiple cytokines is efficacious across a range of IMIDs. By corollary, this effect has potential safety repercussions (see below). Clinical experience with JAKi will likely provide innovative insights to rewrite our understanding of IMIDs.

Among the JAKi currently approved or under study for IMIDs, current information on enzyme assays, cellular assays and in vivo data (see above note on laboratory test results regarding JAK2 inhibition, especially anaemia) suggest that at clinically used doses tofacitinib is preferentially a JAK 1, 3 and 2 inhibitor; baricitinib is primarily a JAK 1 and 2 inhibitor; peficitinib is an inhibitor of JAK3 over JAK 1, 2 and TYK2; upadacitinib is a JAK1 inhibitor with effects on JAK2, and filgotinib is primarily a JAK 1 inhibitor (figure 1).[40] As mentioned above, the preferential selectivity is dose-dependent and decreases with increasing doses as their common mechanism is to prevent ATP-mediated protein tyrosine kinase phosphorylation (although a specific TYK2 selective inhibitor is also under development that inhibits signal transduction by stabilising the pseudokinase domain of the protein).[41]

METHODS

The expert committee adhered to the EULAR standard operating procedures for the development of recommendations.[42] A steering committee comprising 15 members and an expanded Task Force consisting of 14 additional individuals invited based on their expertise and availability and including two patient research partners (MdW, MV) and a health professional (MS-M) as well as a dermatologist (W-HB), a gastroenterologist (MT), a haematologist/haemostaseologist (KG), an infectious disease specialist (KLW) and a fellow who performed the systematic literature review (SLR) (AK), evaluated the available data. The clinicians were all experienced in the treatment of chronic inflammatory diseases, had participated in clinical trials of JAKi and/or bDMARDs, and several had long-standing experience in patient outcomes research and prior consensus statement development. The patients and health professionals all had experience in consensus activities. There was a broad global representation from European countries, Asia, Australia, Latin America and North America. All task force members declared their potential conflicts of interest and had ongoing opportunity to declare if they felt conflicted throughout the process.

Drugs that had not yet undergone regulatory assessment or formal approval but for which evidence from clinical trials was available, could be considered in the recommendations to anticipate potential future uptake in clinical practice, with all

respective caveats that may emerge during the approval process. Indeed, during the time of writing or revising the manuscript (and thus after the face-to-face meetings), two drugs, upadacitnib and most recently filgotinib, were approved (at least in some regions), confirming the validity of the conclusions drawn on these agents in the course of the process developing the consensus statement.

The steering committee and the fellow (AK) initially discussed the research questions for the SLR which was then performed accordingly by searching the totality of the respective clinical trial literature until end of December 2018 in Medline, Embase, Cochrane and 2018 EULAR and ACR abstracts. The details of the SLR are published separately.[43] Cochrane risk of bias tool was used. The SLR addressed RA, PsA, PsO, AS, systemic lupus erythematosus (SLE), UC, CD, alopecia areata (AA)/alopecia universalis, and atopic dermatitis (AD).

The results of the SLR were first presented to the steering group which developed a list of proposed recommendations and/or topics to be addressed by the whole task force. The SLR and the list prepared by the steering group were then presented to the task force which met end of March 2019. Efficacy aspects were discussed by the whole task force with input from experts in respective fields. The Task Force was split into four breakout groups. One group addressed screening, the second monitoring, the third contraindications and the fourth adverse effects. Representatives of each breakout group reported the results of the deliberations and presented proposals for the wording of individual points to the whole task force which discussed them in detail before voting took place.

For a general principle or point of consideration to be accepted for the final document without further change, a majority of 75% of the votes was required in the first ballot. If this result was not achieved, the respective text was amended and subjected to a second ballot, for which a 67% majority was required. If this ballot was not successful, further changes were proposed until a≥50% majority was attained (or the proposal rejected). The points to consider are presented in the wording they were finally voted on (table 1). The results of the respective last ballot are shown as percentage of present members in table 1. Notes captured the contents of the discussions and the reasoning behind each decision to be presented in the comments accompanying the individual items in the manuscript. Data which emerged after the voting process, such as material made public by regulators, were taken into consideration in the manuscript to provide the readers with up-to-date information.

After the face-to-face meeting, the points to consider as agreed by the task force received a final adjudication in terms of level of evidence and strength of recommendation. They were finally subjected to an anonymous vote (by email) on the levels of agreement. Each recommendation received an adjudication on a scale of 0–10, 0 meaning no agreement whatsoever and 10 absolute agreement. The draft of the manuscript was sent to all task force members for their comments which were all considered for the final version prior to submission of the manuscript.

RESULTS

General principles

The task force agreed on four general principles (table 1). The first of these refers to the importance of shared decision making between the patient and the specialist, including information on the benefits and risks of JAKi which is highlighted as principle A. This is in line with various management recommendations but needs to receive special emphasis when a drug or class of medicines is new and long-term experience is still lacking.

The task force further recommends to use these points-to-consider together with general management recommendations for the individual diseases which are usually provided by the respective international or national societies (item B) and also to refer to the product information related to the specific disease to be treated (see below item D).

At outset, the task force decided not to provide 'recommendations' for the use of JAKi in treatment algorithms, but rather 'points to consider' assisting the clinician when thinking of starting, or having decided to start treatment with a JAKi (principle C). Recommendations may be seen as too directive and would have to be brought into the context of other medications and general treatment strategies and adjusted as new information comes to hand in a rapidly evolving therapeutic area. In contrast, the task force saw its role in elucidating important aspects that should be taken into account when thinking of the prescription of a JAKi. To this end, general principles as well as specific considerations are highlighted as an adjunct to product information (principle D).

Individual points

Six major groups of consideration are highlighted (table 1): indications; dosage and comedications; contraindications; pretreatment screening and risks; adverse events; and laboratory and clinical follow-up. The order within these groups does not relate to any ranking by importance but occurred either by chance or some rationale-based approach to therapies in general.

I. Indications

JAKi have proven efficacious with acceptable safety in patients with a variety of IMIDs. They have received regulatory approval for patients with RA, PsA and UC who have failed prior conventional synthetic DMARD (csDMARD) or bDMARD therapy, and an approval is being sought in further indications, such as dermatological, and interferonopathies. Approval of additional JAKi for IMIDs is expected. At present, individual JAKi have been approved for different diseases and at varying doses, as detailed below.

Treatment dose and comedications in different IMIDs

Treatment doses and comedications may differ between indications (see below) and may have to be adjusted with higher age and organ (hepatic, renal) function impairment. Once the therapeutic target (such as remission) is reached, dose reduction or increase of intervals between doses may be considered; this dose adjustment is not within the label of the JAKi, but similar dose changes outside the label have been suggested for bDMARDs in various recommendations.[44 45] In the following, we will address these aspects for the individual IMIDs for which JAKi are approved or may be licensed in the future.

Rheumatoid arthritis

Addition of a JAKi to continued methotrexate (MTX) or other csDMARDs should be considered if the patient tolerates the csDMARD,[44] since—just like for all bDMARDs—there is evidence for better efficacy of combination compared with monotherapy, clinically and/or structurally.[46 47] Monotherapy of JAKi compared with MTX monotherapy in MTX naïve RA patients failed to show significant structural (though not clinical) superiority for baricitinib[47] and—for the primary endpoint—failed to show clinical (though not structural) superiority for

Table 1 Points to consider for the treatment of patients with immune mediated inflammatory diseases with Janus kinase (JAK) inhibitors

Item	Wording	LoE	SoR	Vote (%)	LoA
	General principles*				
A	Initiation of JAK-inhibitor therapy and the treatment target to be achieved should be based on a shared decision between the patient and the medical specialist, which requires full information of the patient on the potential benefit and risks of this therapy.	n.a.	n.a.	100	10
B	Therapeutic approaches to treating patients with chronic inflammatory conditions should be in line with international and national recommendations (algorithms) for the management of the respective disease.	n.a.	n.a.	92	9.5
C	The points to consider when initiating JAK-inhibitor therapy do not provide information on when JAK-inhibitors should be used in the treatment algorithm, but rather attempt to assist the clinician once the decision to prescribe a JAK inhibitor has been made.	n.a.	n.a.	92	9.8
D	These points to consider address specific (but not all) aspects related to the application of JAK-inhibitor therapy and the clinician should additionally refer to the disease-specific product information.	n.a.	n.a.	88	9.8
	Individual points*				
I	***Indications***				
1	Patients with immune mediated inflammatory diseases (IMIDs) who have failed prior conventional and/or biological therapies; as of 2019, these include rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ulcerative colitis (UC).	1a	A	100	9.7
2	Currently, there is no direct evidence of superiority regarding efficacy or safety of one JAK-inhibitor over another one.	5	D	88	9.8
II	***Treatment dose and comedications in different IMIDs***				
1	Use the dose recommended for the specific disease	1a	A	100	9.6
2	Consider dose adjustments in patients with higher age (>70 years), significantly impaired renal or hepatic function and/or risk of drug-interactions, or as a result of other comorbidities, as per individual product information.	2b/5	C/D	100	9.7
3	Regarding comedication, follow specific recommendations for the respective disease; in RA consider adding a JAK inhibitor to continued csDMARDs, if the patient tolerates the csDMARD	1a	A	92	9.1
4	Consider dose reduction of the JAK inhibitor in RA patients in sustained CDAI or Boolean remission on background csDMARDs.	1b	A	77	9
III	***Contraindications*** (consult also label and warning, see general principle D)				
1	Severe active (or chronic) infections, including TB and opportunistic infections.	2b/5	B/D	100	9.9
2	Current malignancies.	5	D	80	9.2
3	Severe organ dysfunction, such as severe hepatic disease (Child-Pugh C) or severe renal disease.	5	D	100	9.9
4	Pregnancy and lactation.	5	D	100	9.9
5	Recurrent VTE (unless anticoagulated)	5	D	93	8.8
IV	***Pre-treatment screening and risks***				
1	Patient history and physical examination.	5	D	100	9.9
2	Routine laboratory testing (full and differential blood counts, liver tests (transaminases), renal function; lipid levels at approximately 3 months after initiation of therapy (and possibly at baseline unless measured within the last 12 months); no CPK testing recommended.	2b/5	B/D	80	9.3
3	Hepatitis B testing (hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and with/without HBV DNA testing as discussed in text). Hepatitis C testing (hepatitis C antibody, with HCV RNA testing if antibody positive)	5	D	92	9.8
4	Human immunodeficiency virus testing in high-risk populations	5	D	100	9.9
5	TB screening as per national guidelines	2b	B	96	9.9
6	Assess and update vaccination status.	5	D	100	9.9
7	Consider risk factors for VTE, especially a past history of VTE.	5	D	96	9.9
V	***Adverse events***				
1	Serious infections (similar to bDMARDs), opportunistic infections including TB, Herpes zoster* (increased rates compared to bDMARDs); the risk of infectious events can be lowered with reduction or elimination of concomitant glucocorticoid use.	2b	B	100	9.9
2	Rates of malignancy do not appear elevated with JAK inhibition, although the risk of NMSC may be elevated.	2b	B	95	9.6
3	Lymphopenia, thrombocytopenia, neutropenia, anaemia may occur.	2b	B	100	9.8
4	An increased risk of VTE has been reported in a safety trial of RA among patients using 10 mg two times a day tofacitinib and within the placebo-controlled trial period of baricitinib in patients with RA.	2b	B	94	9.5
5	Elevations of CPK are noted with JAK inhibitors but have not been associated with clinical events. Elevations of creatinine have been noted with JAK inhibitors but have not been associated with renal failure or hypertension.	2b	B	94	9.5
VI	***Laboratory and clinical monitoring during follow-up.***				
1	Minimal laboratory monitoring: full and differential blood counts and liver transaminase tests at 1 and 3 months and then periodically, such as every 3 months; lipid levels only at month 3.	2b/5	B/D	92	9.4
2	Annual skin examination (for detection of skin cancer).	5	D	83	8.3
3	Evaluate response using validated, disease-specific measures of disease activity; for evaluation and definition of response, be aware that CRP and ESR may be reduced independently of reduction of disease activity and possibly even in infections.	2b/5	B/D	95	9.8

These bullet points have been agreed on as abbreviated summaries of the discussions and the explanatory text to each of these items should be regarded as an integral part of these points.
*These points are a short abbreviation of the items discussed and presented in detail in the body of the text. They should not be applied independently of the information provided there in more detail, but present only an overview of the general scope of the consensus statement. The percentages shown reflect the proportion of participants who approved the respective bullet point during the voting at the task force meeting. Some items carry two levels of evidence, because part of the respective points have only the level of expert opinion (level 5), namely II/2: comorbidities not studied, since most excluded from trials; III/1: patients with chronic infections (even if mild) were not studied; IV/2and VI/1: proposed intervals not studied; VI/3 blunting of the acute phase response during infections not sufficiently studied.
bDMARD, biological disease-modifying antirheumatic drug; CDAI, Crohn's Disease Activity Index; CPK, creatine phosphokinase; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HBV, hepatitis B virus; HCV, hepatitis C virus; LoA, levels of agreement; LoE, level of evidence; n.a., not available; NMSC, non-melanoma skin cancer; SoR, strength of recommendation; TB, tuberculosis; VTE, venous thromboembolism.

filgotinib,[48] while combination therapy achieved significant superiority across all outcomes. On the other hand, monotherapy of tofacitinib and upadacitinib in MTX naïve patients had significantly better clinical and structural efficacy than MTX monotherapy,[49 50] but neither was investigated in 3-arm trials with an additional combination arm. In contrast, filgotinib was

assessed in a 3-arm trial in MTX-naive RA patients; while at both the 100 mg and 200 mg dose filgotinib plus MTX attained the primary endpoint of superiority against MTX monotherapy, filgotinib monotherapy at 200 mg failed to show statistical superiority compared with MTX monotherapy (filgotinib 100mg as monotherapy was not tested), [1 48] None of the JAKi has ever been compared with MTX plus glucocorticoids, the standard therapy recommended by EULAR for over a decade[44] which has not been shown to be inferior to bDMARDs plus MTX.[51 52] However, a JAKi can be given as monotherapy in case of intolerance or contraindications to MTX and other csDMARDs.

The recommended dose of tofacitinib for RA is 5 mg two times a day in most countries; at this dose tofacitinib was superior to placebo in patients with active disease despite MTX or prior bDMARD therapy, and in a head to head study tofacitinib 5 mg two times a day combined with MTX was non-inferior (but not superior) to adalimumab combined with MTX while monotherapy of tofacitinib 5 mg two times a day failed to show non-inferiority to either combination therapy with tofacitinib plus MTX or adalimumab plus MTX.[46] Of note, according to information by regulatory authorities tofacitinib at 10 mg two times a day was associated with an increased venous thromboembolism (VTE) and pulmonary embolism (PE) rate in patients with RA enriched for cardiovascular risk factors,[53 54] and a similar warning was also issued for 5 mg two times a day[55] (see also below). In addition, the dose should be reduced in patients with a creatinine clearance (CrCl) of <30 mL/min and is contraindicated in patients with severe hepatic impairment (Child Pugh C).

The recommended dose of baricitinib in RA is 4 mg once daily (except for some countries such as USA, Canada and China, where it is 2 mg daily). At the 4 mg dose in combination with MTX, it showed superior efficacy to placebo (or de novo MTX) in all RA patient populations, MTX/csDMARD-insufficient responders (IR), bDMARD-IR or MTX-naïve, respectively; in most countries the approval is for these populations apart from MTX-naïve patients, as combination therapy or monotherapy. A dose of 2 mg once daily is appropriate for patients aged ≥75 years, those with a CrCl of 30–60 mL/min and may be appropriate for patients with a history of chronic or recurrent infections. In a head to head study baricitinib 4 mg per day combined with MTX had superior efficacy compared with adalimumab 40 mg combined with MTX.[56] Subanalyses revealed that this superiority was primarily seen for patient reported outcomes, but not for joint counts. In a tapering study patients in long-term low disease activity or remission after 15 months therapy could reduce baricitinib to 2 mg per day; low disease activity (LDA) was maintained at 12 weeks after step down in 83% of patients; 90% of those who flared regained their original response after dose increase.[57] Combination of baricitinib with MTX had significantly better structural outcomes compared with MTX alone, but—while monotherapy was similar to combination therapy in terms of clinical and functional outcomes—structural benefit was not significant for baricitinib monotherapy.[47]

Since the date of the SLR, upadactinib has been approved by FDA and EMA at 15 mg daily. At this dose, it showed superior efficacy to placebo (or de novo MTX) in all RA patient populations, MTX-IR, bDMARD-IR or MTX-naïve, respectively. In most countries, the approval is for these populations except for MTX-naïve, as combination therapy or monotherapy. A upadacitinib monotherapy study in patients with IR to MTX had high response rates but lacked a comparator group of upadacitinib combined with MTX.[49] In combination with MTX, upadacitinib 15 mg provided superior efficacy compared with adalimumab plus MTX in a head to head study.[58] As in the study of baricitinib versus adalimumab, subanalyses revealed that this superiority was primarily seen for patient-reported outcomes, but not for joint counts.[58] No dose adjustment is needed for renal impairment, but with severe hepatic impairment the drug is contraindicated.

More recently, filgotinib was approved at 100 mg and 200 mg doses in Europe[59] and in Japan. In contrast, FDA did not approve filgotinib wishing to await data from spermatogenesis safety studies and raising concern about the safety of the 200 mg dose.[60] Filgotinib has completed phase 3 clinical trials at 100 mg and 200 mg daily. Data of a study comparing filgotinib plus MTX head to head with adalimumab plus MTX recently became available and revealed non-inferiority for DAS28-C reactive protein (CRP) <3.2 for the 200 mg, but not the 100 mg dose; it was not possible to claim superiority versus adalimumab plus MTX due to the statistical plan.[61] Filgotinib has also been studied as monotherapy (see above).

Peficitinib showed significant efficacy on symptoms, signs and structural outcomes of RA in randomised trials including monotherapy and concomitant MTX treatment, in patients with an IR to TNFi and an open label study with etanercept as a safety control. These studies included a majority of Japanese, Korean and Taiwanese patients,[62 63] while the difference to placebo was small in a global study where very high placebo response rates were seen.[64] Peficitinib is approved in Japan and Korea at 100 and 150 mg daily.

The dose of JAKi should be modified according to patient-specific demographics, comorbidities and/or concomitant medications as per product monograph inserts (see also section on contraindications).

There is no evidence at present that one JAKi is more efficacious clinically, functionally or structurally or safer than another JAKi. While two studies have shown superior efficacy of a JAKi plus MTX compared with an anti-TNF plus MTX,[56 58] two other trials have failed to show such effect[46 61]; moreover, in the trials showing superiority of a JAKi plus MTX to adalimumab plus MTX, the significantly better efficacy was seen for most outcomes, but not for tender and swollen joint counts.[56 58] Thus, the relevance of this finding is currently limited; moreover, as of now, no study compared one JAKi with another. On the other hand, several of the above cited studies clearly revealed that JAKi have superior efficacy than TNFi for pain and fatigue, an aspect that deserves further investigation, as it may relate to a hitherto insufficiently recognised and specific mode of action for this drug class.

No studies are yet available in JAKi IR or intolerant patients switching from one JAKi to another JAKi. However, a recent study showed efficacy of anti-TNF therapy after IR to a JAKi,[65] and safety regarding switch from a bDMARD to a JAKi without washout, information that was missing hitherto.

Regarding dose reduction in patients with RA in sustained Clinical Disease Activity Index (CDAI) or Boolean remission on background csDMARD, trial evidence is currently confined to dose reduction for baricitinib.[57]

Psoriatic arthritis

Currently, only tofacitinib is approved for PsA; the licensed dose is 5 mg two times a day. The clinical trials demonstrated efficacy in patients with prior IR to csDMARDs[66] and TNFi.[67] The efficacy in PsO is described below.

Since the closing date of the SLR, two phase 3 trials of upadacitinib were completed successfully, showing efficacy regarding main outcomes of PsA, also when compared with adalimumab

(non-inferiority for the ACR20 response with the 15 mg and superiority with the 30 mg dose).[68 69]

Filgotinib at 200 mg daily showed efficacy in a phase 2 trial[70] and phase 3 data are awaited.

Ankylosing spondylitis

Tofacitinib demonstrated significant efficacy at 12 weeks for signs and symptoms in patients with highly active AS (by modified New York criteria) refractory to NSAIDs in a phase 2 dose-ranging placebo-controlled RCT. The highest Assessment of SpondyloArthritis international Society (ASAS) 20 response was observed at 5 mg two times a day, especially in patients with both elevated CRP and evidence of MRI inflammation in the sacroiliac joints.[71] A dose-dependent effect for clinical response was not evident. Separation from placebo was observed at 4–8 weeks suggesting a slower onset of response than seen with TNFi.

Filgotinib at 200 mg once daily has been assessed in patients with active AS refractory to NSAIDs and TNFi (10%) in a 12 week phase 2 placebo-controlled RCT.[28] Significant benefit for disease activity, assessed by the AS Disease Activity Score (ASDAS), was evident by week 1 and major improvement in ASDAS was noted in 33% versus 2% of patients on filgotinib and placebo, respectively, at 12 weeks. For most outcomes separation from placebo was observed at 4–8 weeks.

Upadacitinib at 15 mg daily was assessed in a 12-week phase 2/3 placebo-controlled trial that recruited patients with active AS refractory to NSAIDs.[72] Significantly more patients had an ASAS 40 response at week 14 in the upadacitinib versus the placebo group (52% vs 26%) and this was observed at the first post-baseline visit at week 2. Other outcomes including MRI spine and sacroiliac joint inflammation, were also superior for upadacitinib, just like for tofacitinib and filgotinib.

Overall, the 12-week phase 2 data support the efficacy of JAKi for a variety of disease outcomes relevant to AS to a degree comparable to TNFi while the pattern of AEs and changes in laboratory outcomes were similar to those reported in previous studies in other indications.

Dermatological diseases including PsO

Nine different JAKi and three selective TYK2 inhibitor have been evaluated in PsO; none of them has been approved for this indication to date except for occasional individual countries, such as Russia (tofacitinib).

Tofacitinib was tested in one phase II, four phase III and one long-term extension study, the results of which were recently summarised.[73] Tofacitinib 5 and 10 mg two times a day showed superiority over placebo for all efficacy endpoints at week 16, with response maintained for 52 weeks of continued treatment. The Psoriasis Area and Severity Score (PASI) response, however, appeared numerically lower than that typically seen for bDMARDs such as IL-12/23 or IL-17 inhibitors. Tofacitinib improved patients' quality of life and was well tolerated. With the exception of herpes zoster, rates of safety events of interest were similar to those in the published literature and healthcare databases for other systemic PsO therapies. Tofacitinib 10 mg two times a day demonstrated greater efficacy (PASI75 at 12 weeks: 43% in MTX-IR and 21% in TNFi patients) than 5 mg two times a day. An additional phase IIa study evaluating topical application of tofacitinib in mild-to-moderate PsO found significant clinical improvement over placebo treatment after 4 weeks.[74]

Baricitinib was studied in a phase IIa dose-ranging study, using once daily dosing over 12 weeks. A statistically significant difference among patients exhibiting at least a 75% improvement in their PASI (PASI75) when compared with placebo was observed for patients receiving 8 or 10 mg daily (43% and 54% vs 17%),[75] a much higher dose than approved for RA and, again even at this dose the skin response is numerically lower than reported for several of the more recently approved bDMARDs; for example, for IL-12/23 inhibitors the PASI75 amounted to about 70% and 80% for ustekinumab and guselkumab, respectively,.[76 77] and to 89% on IL-17 inhibition.[78]

For the JAK1 inhibitors abrocitinib, itacitinib and GSK2586184 as well as the JAK1/3 inhibitor peficitinib, data in the public domain are equally available from one phase II study each. 60% of patients receiving the most effective dose regimen (200 mg twice daily) of abrocitinib experienced a 75% improvement of the PASI.[79] Itacitinib showed significant improvement in the Physician Global Assessment (PGA) after 4 weeks of treatment with 600 mg once daily versus placebo,[80] while GSK2586184 at 400 mg once daily yielded a 75% PASI improvement in 57% of patients after 12 weeks,[81] and patients treated with 50 mg of peficitinib once daily benefitted from improved PASI, PGA and reduced body surface area affected.[82]

Another JAKi, ruxolitinib, was tested in two topical formulations containing 1% and 1.5% of ruxolitinib, respectively, versus placebo and two active comparators, namely calcipotriene 0.005% cream and betamethasone doproprionate 0.05% cream. A statistically significant difference versus the vehicle was observed after 4 weeks of treatment for the ruxolitinib 1% group, with comparable efficacy of ruxolitinib formulations with the active comparators.[83]

For two additional JAKi, no peer-reviewed publicly available data have been published so far.

Finally, a phase II study evaluating the TYK2 inhibitor BMS-986165 was recently published.[41] Doses ranging from 3 mg every other day up to 12 mg daily were studied and compared with placebo. BMS-986165 at doses of 3 mg daily and higher was found to result in greater clearing of PsO than did placebo over a period of 12 weeks, with PASI75 responses up to 75% in the highest dose group. Data for two additional TYK2 inhibitors await peer-reviewed publication.

Evidence for therapeutic efficacy of JAK-inhibitors or TYK2-inhibitors has also been suggested in several other immune-mediated inflammatory dermatoses, including atopic dermatitis, alopecia areata, vitiligo,[84] palmoplantar pustulosis and a case of a mucocutaneous disease called idiopathic erythema multiforme associated with a mutation in *TRPS1* and JAK-STAT activation.[85]

Taken together, PsO belongs to a group of chronic inflammatory skin diseases for which inhibition of JAKs or TYK2 has shown clinical efficacy. However, the extent of efficacy observed and the safety profile of the JAKi has so far not led to drug authorisation by EMA or FDA, but there is considerable interest around TYK2 inhibition, given the absence of some safety issues linked to non-selective JAKi, as well as regarding indications other than PsO, namely AD, where there are still far less options available for systemic therapies.

Inflammatory bowel disease

Tofacitinib is indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.[34] Tofacitinib 5, 10 and 15 mg two times a day showed significant efficacy for remission (Mayo score) in patients who were cs- and bDMARD-IR.[86] The recommended dose is 10 mg given orally twice daily for induction for 8

weeks (or 16 weeks if adequate benefit is not achieved) and 5 mg given twice daily for maintenance (in TNFi-IR patients 10 mg two times a day maintenance may be used). The 10 mg two times a day dose was associated with VTEs and PEs in patients with RA[53] (see also below).

Upadacitinib and peficitinib similarly have shown efficacy in phase 2 trials in csDMARD and bDMARD-IR patients in dose-ranging studies of UC.[87 88]

In CD, tofacitinib at 5–15 mg two times a day has shown no significant efficacy in induction and maintenance of Crohn's disease activity index remission (<150) compared with placebo.[35] However, selective JAK1 inhibition by filgotinib showed increased remission rates in patients with moderate to severe CD.[36] Moreover, upadacitinib also showed promising results in a phase II trial in CD[37] and larger phase III trials have been initiated. Collectively, these findings hold promise for these agents as clinical therapeutics in IBD which await corroboration in ongoing phase III trials.

Other diseases

Baricitinib was investigated in a phase 2 trial of systemic lupus erythematosus and demonstrated significant efficacy at 4 mg but not 2 mg compared with placebo.[89]

Other indications for which JAKi are being evaluated include non-infectious uveitis, CANDLE syndrome and other interferonopathies, including USP18 deficiency.[90–92] The reader is referred to the SLR manuscript.[43]

II. Treatment dose and comedication

1. Use the dose recommended for the specific disease.

The dosing of individual JAKi in the various diseases has been addressed in the previous section (see above).

2. Dose adjustments due to drug interactions

Tofacitinib is metabolised by the hepatic cytochrome P (CYP) 450 pathway which leads to drug interactions with inhibitors such as ketoconazole and promoters such as rifampicin, necessitating dosage adjustments, although it is also 30% renally excreted. In contrast, baricitinib is 70% renally excreted. Filgotinib is metabolised by hepatic carboxylesterases and has a major metabolite GS-829845 which is a pharmacologically active, selective inhibitor of JAK1, but is 10–20 times less potent than the parent compound. Upadacitinib predominantly undergoes hepatic oxidation with minor CYP metabolism and peficitinib undergoes hepatic conjugation. Organic anion transporter 3 inhibitors, such as probenecid, interact with baricitinib requiring a dose reduction to 2 mg per day (with normal renal function). Rifampicin when used in latent tuberculosis (TB) prophylaxis or therapy for active TB increases hepatic metabolism of tofacitinib and upadacitinib so that a dose increase of the latter has to be considered. Ketoconazole has the opposite effect, inhibiting tofacitinib and upadacitinib metabolism so a dose reduction is suggested. Dose adjustments due to hepatic or renal impairment are discussed below.

The dosing of the individual agents and their metabolisation are summarised in table 2.

3. Comedication

Comedication has been addressed in the previous section, including addition of JAKi to pre-existing csDMARDs as combination therapy.

Table 2 Dosing and metabolisation of the different Jakinibs

Drug	Dosage	Approved indications	Metabolism
Tofacitinib	RA, PsA: 5 mg bd, 11 mgs ER daily; UC: 10 mg two times a day	RA, PsA, UC	CyP3A4; 30% renal excretion
Baricitinib	2 or 4 mg daily	RA	>66% renal excretion
Upadacitinib	15 mg daily	RA	CyP3A4; 20% renal excretion
Filgotinib	100 or 200 mg daily	RA	CES2 ; active metabolite 1:10 potency
Peficitinib	100 or 150 mg daily	RA	NNMT, SULT2A1; 16% renal excretion
Ruxolitinib	5–25 mg two times a day	Polycythaemia rubra vera Myelofibrosis	CyP3A4, CyP2C9

CES2, carboxylesteraseisoform 2; Cyp, cytochrome P; ER, extended release ; NNMT, nicotinamide N-methyltransferase; PsA, psoriaticarthritis; RA, rheumatoid arthritis; SULT2A1, sulfotransferase 2A1; UC, ulcerative colitis.

4. Consider dose reduction in sustained remission on background therapy

This aspect has also been addressed in the previous section. For dose adjustments due to impaired organ function see below.

III. Contraindications that should be considered

Contraindications are primarily related to the adverse event and the pharmacokinetic/pharmacodynamic profile of the various JAKi.

1. Severe active infections, acute or chronic, including latent TB and opportunistic: these infections can be seen in patients treated with JAKi.[93] Serious infection rates in RA and PsA studies of tofacitinib, baricitinib and upadacitinib were comparable to adalimumab with higher rates occurring at higher doses.[12 93] Tofacitinib treated RA patients above 65 years (with cardiovascular risk factors) exhibited a higher rate of serious infections compared with TNFi treated patients and according to EMA tofacitinib should be used in these patients only if there is no other alternative.[94] A recently published post hoc analysis of RA trial data that included an adalimumab comparator found similarly increased risks for serious infections among the elderly, particularly among those using 10 mg two times a day tofacitinib. Risk elevations as compared with younger patients were similar for those using adalimumab and tofacitinib 5 mg two times a day, but several fold higher for those using 10 mg two times a day.[95]
2. Malignancy: using a JAKi in this situation should be a shared decision with the patient given timing of past malignancy, uncontrolled malignancy or ongoing treatment with chemotherapy including checkpoint inhibitors. Thus far, patient registries and clinical trial data have demonstrated no malignancy signal. There are no data to suggest that prior malignancy is problematic with JAKi therapy, but most studies excluded patients with malignant disease up to 5 years prior to enrolment.
3. Severe organ dysfunction: With severe hepatic disease (Child-Pugh C), JAKi should not be used. With respect to severe renal disease (CrCl) <30 mL/min), a reduction in dosage is recommended for tofacitinib to 5 mg once daily; baricitinib is not recommended if CrCl is <30mL/min. With CrCl 30–60 mL/min baricitinib should be used at 2 mg daily. No dosage reduction is currently recommended for other JAKi.

4. Pregnancy and lactation: Limited data are available and contraception while taking JAKi is advised for both female and male patients in the absence of adequate data. Tofacitinib has been shown to be teratogenic in rats and rabbits, and to affect parturition and peri/postnatal development.[96]
   Filgotinib reduces spermatogenesis in a dose-dependent manner in animal studies; to date, this has not been observed in humans, but a definitive study evaluating this question is currently underway[97] so this can then be taken into account appropriately in male patients.
   These agents have short plasma half-lives but a gap of 4 weeks is recommended after the last dose if future pregnancy is being contemplated. It is not known whether tofacitinib is secreted in human milk, but it is secreted in the milk of lactating rats. A risk to the breast-fed child therefore cannot be excluded. As a precautionary measure, the use of tofacitinib during breast-feeding is contraindicated.
   A study of a small number of patients with UC taking tofacitinib observed healthy newborns, no foetal deaths or congenital malformations and spontaneous abortions appeared consistent with background risks in the USA.[98] Similar data exist for RA and PsO.[99]
5. History of VTE events: in patients with a history of thromboembolic events initiation of a JAKi should be carefully evaluated based on the increased rates of VTEs in patients at risk for these events (see below under risks and adverse events). Increased VTEs, especially PE, have been observed in patients with cardiovascular risk factors treated with 10 mg tofacitinib two times a day[53 54] indicating that also these (arterial) risks require consideration. Patients with recurrent thromboembolic events will usually receive anticoagulation treatment likely counteracting the risk.

The safety and efficacy of JAKi is under investigation in juvenile patients but has not yet been established in persons <18 years of age. For restrictions regarding patients >65 years of age see below.

Finally, JAKi have not been studied and, therefore, are not recommended in combination with bDMARDs or potent immunosuppressive agents such as cyclosporine or tacrolimus because of the possibility of increased immunosuppression and increased risk of infection or lymphoma.

IV. Pretreatment screening and risk assessments

1. History and physical examination: Important patient details to obtain before starting therapy include a history and risk estimation of VTE, infections, TB, risk factors for hepatitis B and C, as well as usual medical considerations such as comorbidities, cardiovascular risk factors and concomitant medications of relevance, for example, Cox 2 inhibitors, prednisone doses >7.5 mg daily or oral contraceptives.
   The recommendation for patients over 70 years of age is a baricitinib dose reduction to 2 mg daily due to age-related reductions in renal function. Moreover, EMA has restricted the use of tofacitinib in people older than 65 years also due to an increased risk of serious infections.[94] No dose reduction is recommended for modest renal impairment with upadacitinib and filgotinib therapy.
   Baseline skin check for non-melanoma skin cancer (NMSC) in patients at risk and chest X-ray is also recommended, unless recently performed.
2. Routine laboratory testing that includes a full blood count (including a differential white cell count), liver enzymes (in particular transaminases), and renal function tests are recommended before starting JAKi. Baseline lipid levels are suggested unless recently checked. No creatine phosphokinase (CPK) testing is needed.
3. Hepatitis B virus (HBV) testing for anti-HBs, anti-HBc, and HBsAg is recommended in all patients. Patients with evidence of chronic HBV infection (ie, positive HBsAg) should avoid JAKi or treatment with biologics if possible. If not possible, then concomitant treatment or prophylaxis with an anti-viral (eg, entecavir, tenofovir or tenofovir alafenamide) should be undertaken alongside consultation with a hepatologist.[100] For patients with evidence of prior HBV exposure (positive HBc antibody) and no evidence of active viral replication (ie, negative HBsAg), a baseline HBV DNA should be obtained to rule out occult active HBV infection. If positive, then patients have active HBV and should be managed according to the above. The main virological event of concern in these anti-HBc positive patients is HBsAg reappearance (seroreversion), consistently associated with hepatitis flare; HBV DNA detection (without HbsAg) leads to seroreversion and hepatitis in 50% of cases.[100] If HBV-DNA negative, then such patients can start JAKi and should be routinely monitored for HBV DNA and HBsAg reappearance (seroreversion) in line with respective national recommendations for TNFi. If HBV DNA or HBsAg subsequently turns positive during monitoring, then the patient should be managed as above with referral to a hepatologist for treatment. The JAKi should be temporarily stopped until full evaluation can be made. Concurrent treatment with an antiviral is possible, and the JAKi can be reinstituted once anti-viral therapy has been started.[101]
   Hepatitis C virus (HCV) antibody testing is recommended and should be further assessed if positive, that is, HCV RNA testing. If positive, then the patient has active HCV and should be referred for treatment. In such case, JAKi should be withheld until HCV treatment has been completed.
4. HIV testing is recommended for those with HIV risk factors.
5. As the risk for TB-reactivation with JAKi is similar to that for TNFi, screening for TB is recommended, unless already done prior to bDMARD commencement without a risk of exposure since then. All patients in JAKi phase 3 studies were screened for TB and patients with active TB excluded while patients with latent TB were commenced on anti-TB therapy and included. Cases of TB were noted with JAKi more commonly than with placebo in pivotal trials, with at least some cases occurring in endemic areas likely representing newly acquired infection rather than reactivation of prior infection.[12 93]
6. Vaccination status should be sought. Country and regional vaccination guidelines should be followed. EULAR has recently updated its vaccination recommendations for patients with autoimmune diseases.[102] In addition to Herpes zoster reactivation, Herpes simplex and cytomegalovirus reactivation may also occur. HPV reactivation is not known to occur, but has not been evaluated systematically.
   Herpes zoster reactivation: A history of varicella or zoster infection or immunisation should be obtained. Herpes zoster reactivation is clearly increased under JAKi with incidence rates (IRs) between 3–4 (Western Europe, USA, Australia) and 9 (Japan, Korea) per 100 patient-years compared with 2–3 per 100 patient-years for TNFi. Risk factors include age, female gender, prednisolone >7.5 mg per day, infection and hospitalisation.[11 12 103–106] As for serious infections, there is also a dose response for Herpes zoster reactivation. The reactivation is likely based on the mode of action of JAKi blocking interferon pathways. If a patient develops Herpes zoster,

JAKi treatment should be temporarily interrupted until the episode resolves. A small proportion of patients can develop recurrent zoster. Antiviral prophylaxis could be considered in such individuals.

Evidence for the efficacy of the live Zostavax vaccine is questionable and as a live attenuated vaccine it necessitates a delay of 3–4 weeks postvaccination before starting a JAKi; further, a single missed dose of MTX could be considered, since MTX may blunt the antibody response,[107] but this approach is not evidence based. In a live zoster vaccination study, zoster IRs at follow-up were numerically similar in the tofacitinib 5 mg and adalimumab and MTX arms but higher rates were seen for the combination of tofacitinib 5 mg two times a day with MTX.[108] Notably, zoster rates at follow-up were generally similar in vaccinated versus non-vaccinated patients, but further studies are clearly needed. While the vaccination resulted in reasonable immune responses, 1 patient developed zoster infection having had no prior immunity.[109]

A new zoster vaccine has been more recently approved; being a nonlive vaccine, it is not contraindicated in patients receiving immunosuppressive or immunomodulating agents, but currently there are no data on safety and protective immunogenicity of this vaccine in patients treated with JAKi. As studies are underway, these questions should be resolved soon. The safety of the inactivated zoster vaccine (Shingrix) has been suggested by a small open label study of 400 patients with RA (no zoster activation, 6.7% disease flares, mostly mild, self-limiting, and not requiring therapeutic change), but efficacy and immunogenicity of the vaccine in this setting is unknown.[110]

7. Risk factors for VTEs[111 112] should be considered by history and a potential clotting abnormality should be pondered in patients with a history of VTEs in whom such assessments have not yet been done. While these events are rare, the risks are increased in patients with prior VTEs; with increasing age (patients older than 65 years are at higher risk for having VTEs with tofacitinib); obesity (people with obesity have two times the risk of VTEs as people with normal weight, and the higher the weight, the higher the risk); prolonged immobility (ie, long travel, lower-extremity paralysis due to spinal cord injury, trauma with reduced mobility); hereditary (ie, factor V Leiden, prothrombin mutation 20210, etc) and acquired (ie, antiphospholipid syndrome, malignancy) thrombophilia; Cox 2 inhibitor therapy[113 114]; prednisolone of ≥7.5 mg/d and above; major surgical interventions, such as neurosurgic, urologic, gynaecologic and orthopedic surgery. Interestingly, a recent study from Sweden suggested that VTEs are significantly related to disease activity with an adjusted RR of 1.99 during high, 1.45 during moderate and 1.11 with low RA activity compared with remission.[114 115] This potential relation between VTE rates and RA disease activity remains to be fully elucidated. For more details regarding VTEs and PEs see below under adverse events.

V. Adverse events

Adverse events are mainly related to the inhibition of cellular pathways and include those already mentioned above under risks. However, several other adverse events need more detailed consideration.

1. Serious infections including opportunistic infections such as TB and others, as well as reactivation of Herpes zoster and other viruses can occur. The IR of Herpes zoster reactivation amounts to about 3–4 compared with placebo (IR=1).[115 116] Their frequency is dose and co-medication dependent and the reactivation of Herpes zoster is more frequent than on bDMARDs and especially frequent in Japan and Korea. Moreover, EMA (but not FDA) has restricted the use of tofacitinib in people older than 65 years due to an increased risk of serious infections.[94] Herpes zoster was also seen with baricitinib and less commonly with upadacitinib. It is also listed as an important potential risk for filgotinib by EMA, and while they state that no signal for varicella zoster infection has been detected in the filgotinib RA clinical trial program, the agency requests further evaluation by additional pharmacovigilance activities.[117]
2. Malignancy: The overall rates are not increased except for the risk of NMSC which might be elevated and, therefore, the task force recommends regular skin examinations, especially in countries with increased risk of NMSC, such as Australia. The task force also felt that current malignancy (except NMSC and cervical carcinoma in situ undergoing treatment) may be a contraindication for JAKi, but as stated previouly, this should be a shared decision making with the patient.
3. Anaemia and cytopenias: Anaemia of chronic disease, as usually seen in most IMIDs, does not improve on the group level with all JAKi except for filgotinib, and in some patients the pre-existing anaemia may deteriorate, presumably due to JAK 2 inhibition; JAK 2 is involved in EPO signalling (see figure 1). Cytopenias may occur but were not more frequent than on placebo,[12] although with all JAKi a few patients may exhibit neutropenia and/or lymphopenia.
4. VTE/pulmonary embolism (PE). Across indications, in randomised controlled trials and long term extensions of tofacitinib followed for up to 9.5 years, no increased risk of VTE for the 5 mg bd dose has been seen.[11 54] However, in a still ongoing safety study of patients with RA enriched for cardiovascular risk factors, a statistically significant PE imbalance for tofacitinib 10 mg bd as compared with 5 mg two times a day was demonstrated with an absolute IR of 0.5 for 10 mg and 0.3 for 5 mg[53–55]; compared with TNFi (absolute IR of 0.1) which were investigated as a control arm, the PE risk thus being about threefold higher for the 5 mg dose and about sixfold higher for the 10 mg dose.[54 94] In this same study, as reported by the EMA, VTE without PE were somewhat numerically higher with tofacitinib than TNFi but the difference was not statistically significant. Since this is an ongoing study, the full data for the 5 mg dose will have to be awaited for a full assessment of the VTE risk, but the 10 mg two times a day dose was discontinued in this study. A recent analysis of VTE/PE in clinical trials of UC in which most of the patients had been treated with a dose of 10 mg two times a day reported that during the placebo controlled period no UC patient had a VTE or PE and 1 VTE and 1 PE each were seen in placebo treated patients.[118] During the long term, open-label extension comprising about 2400 patient-years of exposure, 1 patient had a VTE and 4 had PEs, all with risk factors for these events.[118] The recent EMA assessment provided evidence for an increased PE risk at the 5 mg and especially the 10 mg two times a day dose of tofacitinib.[55] The FDA has not made a final determination and is awaiting the final, adjudicated results of the study.

   Baricitinib at 4 mg had an imbalance in VTEs compared with the control arms (placebo or adalimumab) in the controlled period of RA trials; this has not been observed with the 2 mg dose.[49 119] Risk factors were age, high BMI, immobilisation, surgery, use of Cox-2 inhibitors and a history of prior VTEs;

the risk may be up to 10-fold for patients with a history of VTEs and twofold for those patients taking Cox2 inhibitors.[120] Subsequently, there was no increase in risk when patients were transitioned from placebo or MTX to baricitinib as well as across long-term extension studies over 6 years but VTEs in the LTE were observed equally with 2 and 4 mg. Numerically increased rates of VTEs have also been observed in the double blind phases of upadacitinib trials, primarily with the 15 mg once a day dose, although not in the head-to-head trial against adalimumab.[49 58 119] With respect to filgotinib, EMA regards VTE as a potential risk, but the agency also concluded that no increase in reports of VTEs was seen for filgotinib (100 mg and 200 mg doses) compared to placebo or comparators (MTX, ADA). Importantly, however, additional data by pharmacovigilance activities have been required by EMA.

Taken together, these observations elicited warnings (in some countries "black box" warnings) for VTE in the labels of all approved JAKi, plus additional warnings issued by the regulators (see above). In particular, the EMA recommends the use of tofacitinib in patients with RA 'above the age of 65 only when there is no alternative treatment'.[53 55] Such age considerations have not been set in place for other JAKi that have similar VTE warnings in their label; however, data on outcomes studies in patients with cardiovascular risk factors are not available for those other agents. VTEs on baricitinib also occurred in patients with risk factors, such as obesity, and several continued therapy, although mostly under anticoagulation.[120]

While the overall risk of VTE is age dependent and in the order of 1:100–1:1000 (occurrence rate 0.25/100 patient years), this risk is about doubled in patients with RA.[55] Further research is needed to delineate the mechanisms how JAKi increases VTE rates (and how this compares to patients with RA in general), while we also lack understanding how glucocorticoids, Cox2 inhibitors, oral contraceptives, tamoxifen, thalidomide, antipsychotics elevate VTE risk. In any event, careful consideration should be given as whether or not to start a JAKi in any patient who may be at risk for a VTE.

With respect to major adverse cardiovascular events (MACE) across indications, in randomised controlled trials and long-term extensions no increased risks have been observed. As indicated above, a long-term study of tofacitinib in RA patients with cardiovascular risks is ongoing and has hitherto not shown evidence for an increase in MACE (regarding increase in VTEs see above).

5. Laboratory abnormalities without clinical sequelae in the majority of patients: CPK elevations are occasionally seen without weakness, thus far with occasional myalgia,[121 122] but usually without clinical repercussions, although one patient has had rhabdomyolysis.[123] Thus, in the rare event of symptoms, CPK should be tested, although in general this is not necessary. While the underlying cause is unknown and there have been suggestions this may be due to a renal tubular effect, there are some data suggesting this effect might be due to restoration of muscle development with associated CPK elevations (an event that is suppressed by oncostatin M whose signalling depends on JAKs).[124 125] Creatinine increases have also been observed but without organ dysfunction or other clinical sequelae, such as hypertension.

Finally, gastrointestinal perforation has been reported in clinical trials and may be a risk of bariticitinb and tofacitinib[126] (and possibly other JAKi). Thus, JAKi should be used with caution in patients who may be at increased risk for gastrointestinal perforation (eg, patients with a history of diverticulitis and taking concomitant NSAIDs or glucocorticoids). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation knowing fever and elevation of acute phase reactants may be blunted by JAKi therapy.

VI. Laboratory and clinical monitoring during follow-up

1. As a minimal laboratory monitoring during follow-up, the task force recommends measurement of full blood count and differential, transaminases, renal function, at 1 month and 3 months and then periodically such as every 3 months plus lipid levels just at 3 months.

   Blood count: Haemoglobin change of less than or equal to 20g/L decrease and haemoglobin levels greater than or equal to 90g/L do not require dose adjustment. Greater than a 20g/L decrease or a haemoglobin of less than 80g/L (confirmed by repeat testing) should lead to dose interruption until haemoglobin values have normalised. Filgotinib leads to small dose dependent average increase in haemoglobin levels, compared with all other JAKi.

   Absolute neutrophil counts over 1000/mm^3 require no dose adjustment, however, a count of 500–1000/mm^3 on two sequential measures suggest dose reduction or temporary cessation until count above 1000/mm^3 when JAKi can be recommenced.

   Absolute lymphocyte counts over 750/mm^3 require no dose adjustment, a count of 500–750/mm^3 on two sequential measures suggests a dose reduction or temporary cessation until the count is greater than 750/mm^3 to allow recommencement. There is some evidence that lymphocyte counts below 500/mm^3 significantly increase the risk of opportunistic infection.

   Liver function tests: Transaminases should be periodically monitored. Tofacitinib should not be used in severe hepatic impairment (Child Pugh C) nor should upadacitinib. Mild hepatic impairment (Child Pugh A) requires no dose adjustment. In case of moderate hepatic impairment (Child Pugh B) the tofacitinib dose should be reduced to 5 mg once a day.

   Renal function: Creatinine should be assessed periodically. In mild to moderate chronic renal impairment (CrCL 50–80 mL/min) no dose adjustment is needed; with CrCL 30–60 mL/min, baricitinib should be reduced to 2 mg daily. With severe renal impairment (CrCl <30 mL/min) tofacitinib dose should be reduced to 5 mg once daily and baricitinib not used at all.

   Acute phase reactants: For evaluation and definition of response be aware that CRP and ESR may be reduced independently of reduction of disease activity and, therefore, consideration should be given to the use of disease activity scores that do not include inflammatory markers (such as CDAI in RA; see below under 3).

   Lipid levels should be assessed approximately 3 months after JAKi commencement and if increased should be managed according to national guidelines.
2. Consideration should be given to an annual formal skin check as evidence suggests an increased risk of NMSC with tofacitinib, possibly due to prior exposure to MTX and TNFi.[127]
3. Disease activity should be monitored regularly using validated composite measures of disease activity that include joint counts in order to assess if improvement by >50% was seen within 3 months and the treatment target by 6 months

(treat-to-target),[128 129] in line with current management recommendations for RA and PsA,[2 44] and in line with recommendations for other IMIDs, respectively. It should be borne in mind that acute phase reactant levels may be reduced by JAKi independent of clinical improvement and, therefore, scores that are heavily weighted on acute phase reactants, such as the DAS28, should not be used for follow-up.[130]

Consideration of patient preferences

In rheumatology, there is still a substantial number of patients with suboptimal outcomes or who are faced with uncontrollable disease symptoms. They fail to respond adequately to existing DMARDs. Therefore, the advent of DMARDs with a new mode of action is welcome. The oral route may enable some patients to become more independent from hospital or health professionals compared with subcutaneous injections or infusions and also appeals to those with a needle phobia; on the other hand, some biological agents are only administered monthly or even less frequently and this may be seen as an advantage compared with taking a drug once or twice daily. Cost considerations are an overarching principle in RA treatment recommendations and thus part of treatment decisions; while the costs of JAKi are currently usually higher than those for biosimilars, this may change once these drugs become generic. Careful consideration of initiation and open communication with the patient are warranted. The prescription of JAKi may not be at the expense of attention to safety risks and must be in line with existing specialty guidelines for management and good clinical practice which also includes the need for regular laboratory monitoring even in patients receiving JAKi monotherapy. These points to consider contain important information for patients. A patient version or a decision tool will support patients to weigh potential benefits, harms and their personal goals and preferences, and subsequently strengthen their role in the decision-making process.

Research agenda

The committee felt that many questions remained open and needed to be addressed in future research in both adult and paediatric populations. These questions are pertinent to all JAKi and are presented in box 1.

Box 1 Research agenda

1. What is the efficacy and safety of switching between JAK-inhibitors in non-responders or due to lack of tolerability?
2. What are the predictors of response to JAK-inhibitors as compared to other DMARDs used for RA?
3. What is the effect of JAK-inhibitors on comorbidities of IMIDs including cardiovascular disease and osteoporosis?
4. Is VTE a class effect or a JAK inhibition effect and what is the mechanism of VTE? What is the actual risk of VTE when treating with a JAK-inhibitor? Is the effect confined to RA or observed in other indications?
5. What is the long-term safety from real-world data for JAK-inhibitors? For which patients should JAK inhibitors be contraindicated on basis of risk (particularly for VTE), and should prophylaxis be considered?
6. What is the safety of JAK-inhibition in patients with prior, current or who develop a malignancy whilst on therapy?
7. Are JAK-inhibitors effective and safe as therapy for autoimmune diseases induced by checkpoint inhibitors in patients with malignancy?
8. How safe are JAK-inhibitors in Hepatitis B, C, SARS-CoV-2 infected patients and also other viral infections?
9. How safe are JAK-inhibitors in pregnancy and lactation? What should be recommended if a woman taking a JAK-inhibitor becomes pregnant?
10. Safety of JAK-inhibitors in elective surgery—should they be discontinued and if so for how long and when should they be restarted?
11. What is the efficacy of JAK-inhibitors in extra-articular RA manifestations including vasculitis, nodulosis, overlap syndromes?
12. What is the efficacy of JAK-inhibitors in connective tissue diseases such as SLE, inflammatory myositis and systemic sclerosis?
13. What is the efficacy and safety of combination therapies with JAK-inhibitors and bDMARDs in patients with severe RA or other diseases?
14. What are the molecular in vivo down-stream effects of JAK-inhibition in the setting of individual diseases?
15. What are the differences between different JAK-inhibitors regarding efficacy and safety?
16. What is safety of JAK inhibitors in patients over 65 years?

DISCUSSION

Similar to the situation with bDMARDs 15–20 years ago, real-world experience with JAKi is limited. Therefore, this task force was formed which consisted of experienced clinical trialists and people involved in treating patients with IMIDs across several medical areas and across nations and continents as well as patients and a health professional. The task force set out to provide the readers with comprehensive guidance on the use of this novel class of targeted therapies regarding efficacy and safety, based on evidence and complemented by expert opinion. In this consensus statement points to consider are provided for the use of JAKi across IMIDs for which they are approved or may be approved in the near future.

The consensus statement is designed to support physicians and other health professionals treating patients with IMIDs as well as patients themselves and other stakeholders, such as hospital administrators and payers, with an up-to-date summary on the thoughtful application of JAKi. Where there is occasional redundancy in the paper, it derives from the fact that certain pieces of information relate to more than one chapter of this consensus statement, thus allowing readers who only focus on selected portions to obtain pertinent information.

Currently baricitinib, filgotinib (in Europe and Japan), peficitinib (in Japan), tofacitinib and upadacitinib are licensed for one or more autoimmune inflammatory diseases. The consensus statement is primarily based on the evidence derived by an SLR[43] from clinical trials and some observational studies, whereby safety aspects can currently be primarily or solely derived from information of the controlled and extended trial periods of the drugs.

Indeed, efficacy data from comprehensive clinical trial programmes but hardly any long-term registry data from clinical practice are available on safety aspects . However, trial efficacy and safety data are constantly being expanded, as are the indications. At present five available JAKi are approved for use in RA patients, but tofacitinib is already licensed for PsA and UC and other compounds will also likely receive approval for a range of indications. Thus, JAKi may arrive at a similarly

broad or even broader list of indications across IMIDs as TNF-blockers. However, their broad efficacy is unrelated to inhibition of TNF signalling, but rather due to the fact that the intracellular blockade of JAKs relates to cytokines that are distinctly involved in different IMIDs, such as IL-6 in RA, IL-23 in PsA, PsO and IBD, or interferons in other diseases. Moreover, even if none of the cytokines activating the JAK-STAT pathway is known to be of significance in the pathogenesis of a particular disease, such as axial spondyloarthritis, it is possible that there are synergistic inhibitory effects by interfering with signalling of several cytokines that individually are only minimally pathogenetically relevant, culminating in clinical efficacy. Moreover, JAKi also interfere with the consequences of JAK activation induced by cytokines that do not directly use the JAK-STAT pathway for signalling, such as TNF, which can activate IL-6 and interferons downstream of their primary effects, thus affecting various pathogenic pathways.[39]

There are some differences between the drugs which are due to different selectivities regarding JAKi when looking at both in vivo and in vitro data, spanning from predominant JAK1 inhibition (filgotinib) to pan-JAKi (peficitinib, tofacitinib); these may translate into differences in reversible cytokine inhibition over the dosing period. These differences will be dose dependent[19] and may be reflected in variability in safety but also aspects of efficacy.

Recommendations on indications and dosages can easily be derived from the clinical trials and labels of the respective drugs as stipulated by regulators, but the presumably more important items within this consensus statement relate to contraindications, pretreatment screening, safety and risks as well as monitoring and follow-up examinations. All these items have been addressed. The recommendations may change once further pharmacovigilance and registry data become available. They may also change once more information becomes known regarding pathways to disease or pathways leading to adverse events. Of note, the task force was informed by, and developed its recommendations based on, a detailed SLR evaluating studies that were published until the end of 2018; however, since then additional safety aspects became known from information provided by regulators, but the trial(s) on which this new safety information is based have not yet been published. Thus, the task force went beyond the data provided in the SLR and addressed publications and regulatory communications that appeared after the end of the SLR period to provide readers with the most up-to-date material.

Among the adverse events, some have been expected from knowledge regarding blockade of cytokines that use JAK-STATs for signalling, such as an increased risk of serious (including opportunistic) infections. Others go beyond expectations but are explained by the pharmacologic effects of the drugs, such as the increase in herpes zoster rates. The failure to reverse anaemia of chronic disease would also be in line with expectations based on inhibition of JAK2, and this conclusion is confirmed by the improvement of anaemia when a more selective JAK1 inhibitor is applied.[131] However, even if relatively rare and associated with known risk factors, the occurrence of VTEs and PEs is an unexpected and hitherto unexplained event requiring further information and elucidation. It is not clear if idiosyncratic platelet activation, changes in procoagulant or fibrinolytic activity, or abnormal endothelial activation might be involved. However, other tyrosine kinase inhibitors may activate procoagulant activity[132] which might be related to changes in lipids or lipoprotein levels.[133] During the deliberations of the task force, comments arose that the control arms of some pivotal studies had an unusually low IR of VTEs; nonetheless, it is the nature of randomised controlled trials that the risk should be balanced across study arms and if one arm differs, one may conclude that the results are a consequence of the respective treatment. Further research activities in this area are urgently needed.

Since the time of the SLR, the task force meetings and the start of preparing this manuscript, the COVID-19 pandemic has struck the world. Many patients with IMIDs who are treated with bDMARDs or JAKi have contracted this viral disease. Currently, there is insufficient knowledge about the risks (or potential benefits) of immunomodulating drugs in these patients in either altering susceptibility to infection, or in determining disease progression once infected with SRAS-CoV2. Case reports and individual centre's experiences do not yet suggest that these patients are at increased risk of having an adverse outcome of COVID-19. However, as yet no systematic analyses have been performed to inform physicians whether JAKi therapy may be continued or should be stopped prior to or during infection. Regardless, since these patients may be at an increased risk, primary prevention should be stressed with rigorous application of recommended public health and behavioural measures applied, including physical distancing, wearing masks and hygienic measures as recommended by most governments worldwide. Prophylactic discontinuation of an effective anti-inflammatory or immune modulatory therapy is not recommended at this time.[134–136] However, if therapy has been temporarily ceased in IMID patients with proven COVID-19 infection, when to safely recommence therapy is also not known for patients that have recovered. It is suggested that when oropharyngeal PCR swabs are negative virus shed after a further 7 days may be non-viable.[137]

To better understand the consequences of COVID-19 on IMID patients with and without specific therapies, it is critical to enter patients infected with SARS-CoV2 into relevant registries and several exist.[138–140] Of note, JAKi has been suggested to be potentially beneficial against COVID-19, particularly in the context of the cytokine release syndrome like hyperinflammation which occurs in a small subset of patients, and several trials are currently ongoing to learn whether this approach has positive, negative or neutral effects.[141–144] A rationale for the potential efficacy of baricitinib has been recently provided by Stebbing *et al* and based on predicted interference with viral trafficking.[145] However, answers to the clinical validity of these hypotheses must come from observational studies as well as properly performed clinical trials.

In summary, JAKi are a new class of agents for the treatment of a variety of IMIDs with efficacy in many indications that is at least as good as that of bDMARDs and with an acceptable safety profile. Given their non-protein nature, antidrug antibodies and thus a potential secondary loss of efficacy would not occur. It is anticipated that based on these qualities and on the fact that they can be taken by the oral route their use will significantly increase over time. The presented consensus statement may be particularly helpful to those prescribing these drugs who aim to achieve the most appropriate and optimal use of these therapies.

Author affiliations
[1]School of Medicine, Griffith University, Brisbane, Queensland, Australia
[2]Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, 1090 Vienna, Austria
[3]Dept. Med./Rheumatology and Clinical Immunology, Charite Univ. Hospital, Berlin, Germany
[4]Hopital Cochin, Rheumatology, Université Paris Descartes, Paris, France
[5]Department of Medicine, Southwestern University of Texas, Dallas, Texas, USA
[6]Hietzing Hospital, Wien, Austria

[7]Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK
[8]Medicine, Division of Rheumatology, The University of Western Ontario, London, Ontario, Canada
[9]Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[10]Section for Outcomes Research, Center for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna, Austria
[11]Rheumatology, Keio Univ, School of Medicine, Tokyo, Japan
[12]Division of Gastroenterology and Hepatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria
[13]Oregon Health Sciences University, Portland, Oregon, USA
[14]Medical Humanities, Amsterdam University Medical Centre, Amsterdam, Netherlands
[15]Rheumazentrum Ruhrgebiet, Herne, Germany
[16]Dermatology, University Hospitals of Geneva, Geneva, Switzerland
[17]Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds, UK
[18]Musculoskeletal Research Group, Newcastle University, Newcastle upon Tyne, UK
[19]Rheumatology, Albany Medical College, Albany, New York, USA
[20]Internal Medicine, Seoul National University College of Medicine, Seoul, Korea (the Republic of)
[21]Medicine, University of Alberta Faculty of Medicine and Dentistry, Edmonton, Alberta, Canada
[22]Department of Medicine & Therapeutics, Chinese University of Hong Kong Shaw College, New Territories, Hong Kong
[23]First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan
[24]Rheumatology, University Hospital Gent, Gent, Belgium
[25]KU Leuven University Hospitals Leuven, Leuven, Belgium
[26]Division of Rheumatology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

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ORCID iDs
Peter Nash http://orcid.org/0000-0002-2571-788X
Andreas Kerschbaumer http://orcid.org/0000-0002-6685-8873
Thomas Dörner http://orcid.org/0000-0002-6478-7725
Roy M Fleischmann http://orcid.org/0000-0002-6630-1477
Janet E Pope http://orcid.org/0000-0003-1479-5302
Désirée van der Heijde http://orcid.org/0000-0002-5781-158X
Kevin L Winthrop http://orcid.org/0000-0002-3892-6947
Maarten de Wit http://orcid.org/0000-0002-8428-6354
Daniel Aletaha http://orcid.org/0000-0003-2108-0030
Paul Emery http://orcid.org/0000-0002-7429-8482
Eun Bong Lee http://orcid.org/0000-0003-0703-1208
Walter P Maksymowych http://orcid.org/0000-0002-1291-1755
Yoshiya Tanaka http://orcid.org/0000-0002-0807-7139
René Westhovens http://orcid.org/0000-0002-3432-3073
Josef S Smolen http://orcid.org/0000-0002-4302-8877

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Preliminary predictive criteria for COVID-19 cytokine storm

Roberto Caricchio ,[1] Marcello Gallucci ,[2] Chandra Dass,[3] Xinyan Zhang,[1] Stefania Gallucci ,[4] David Fleece,[5] Michael Bromberg,[6] Gerard J Criner,[7] Temple University COVID-19 Research Group

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For numbered affiliations see end of article.

Correspondence to
Professor Roberto Caricchio, Medicine/Rheumatology, Temple University School of Medicine, Philadelphia, PA 19140, USA; roc@temple.edu

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ABSTRACT

Objectives To develop predictive criteria for COVID-19-associated cytokine storm (CS), a severe hyperimmune response that results in organ damage in some patients infected with COVID-19. We hypothesised that criteria for inflammation and cell death would predict this type of CS.

Methods We analysed 513 hospitalised patients who were positive for COVID-19 reverse transcriptase PCR and for ground-glass opacity by chest high-resolution CT. To achieve an early diagnosis, we analysed the laboratory results of the first 7 days of hospitalisation. We implemented logistic regression and principal component analysis to determine the predictive criteria. We used a 'genetic algorithm' to derive the cut-offs for each laboratory result. We validated the criteria with a second cohort of 258 patients.

Results We found that the criteria for macrophage activation syndrome, haemophagocytic lymphohistiocytosis and the HScore did not identify the COVID-19 cytokine storm (COVID-CS). We developed new predictive criteria, with sensitivity and specificity of 0.85 and 0.80, respectively, comprising three clusters of laboratory results that involve (1) inflammation, (2) cell death and tissue damage, and (3) prerenal electrolyte imbalance. The criteria identified patients with longer hospitalisation and increased mortality. These results highlight the relevance of hyperinflammation and tissue damage in the COVID-CS.

Conclusions We propose new early predictive criteria to identify the CS occurring in patients with COVID-19. The criteria can be readily used in clinical practice to determine the need for an early therapeutic regimen, block the hyperimmune response and possibly decrease mortality.

INTRODUCTION

COVID-19 is the cause of the pandemic declared by the WHO in January 2020.[1] As of 3 August 2020, there have been 18 million confirmed cases and 688 000 deaths worldwide (coronavirus.jhu.edu). While most of these cases are mild, a sizeable number of patients develop a severe acute hyperimmune response characterised by a cytokine storm (CS).[2] Previous epidemics induced by coronaviruses SARS-CoV-1 and Middle Eastern respiratory syndrome-CoV were also associated with a CS.[3] CS occurs in several conditions, including autoimmune diseases, malignancies and infections.[2] Two forms of CS, haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), rely on well-established criteria to identify their occurrence.[4 5] Results from recent reports suggest that COVID-19-associated CS is a unique form of a hyperinflammatory response, which needs further clinical and laboratory characterisation as well as classification criteria.[6] It has been suggested that the 2016 MAS classification criteria are not applicable to patients with COVID-19,[7–9] while it remains to be determined whether the 2004 HLH criteria and the HScore may be more helpful.[10–12] Reports from COVID-19 cohorts and autopsies highlight significant diffuse inflammation and widespread tissue damage, such as renal, cardiac and muscular damage, in addition to pulmonary impairment.[13–17] These findings underscore the need for criteria that should include not only the respiratory status but also markers of inflammation and tissue damage. The latter were recently reported to be associated with higher mortality in COVID-19.[18] We therefore designed a novel statistical strategy based on our clinical experience at Temple University Hospital[19] and developed preliminary criteria that can be used to identify the CS during COVID-19 infection.

METHODS

Patients and data collection

The first cohort used in this study included patients admitted to Temple University Hospital from 10 March 2020 to 17 April 2020. The 513 patients enrolled in the cohort and considered eligible must have met the following criteria on hospital admission: (1) signs and symptoms of COVID-19 infection (fever, generalised malaise, cough and shortness of breath) up to 1 week prior to hospital admission[20] and (2) presence of ground-glass opacity (GGO) by high-resolution CT (HRCT) of the chest as per radiology reading and reverse transcriptase PCR (RT-PCR) for COVID-19 RNA. A positive RT-PCR was not required due to the high percentage (15%) of false negatives in our cohort and in the literature.[21]

Age, sex, race/ethnicity and comorbidities were all collected on admission. Sixty-two laboratory variables, such as complete blood count with differential, complete metabolic panel, inflammatory and respiratory markers, were collected daily. Interleukin (IL)-6 was measured only in a subset of patients, before any biological treatment.

All 513 patients received oxygen supplementation, low-dose (0.5 mg/kg) prednisone and azithromycin

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on admission and for at least the first 7 days of hospitalisation. Eighty-two patients were enrolled in clinical trials with biologics and their laboratory results were initially included in the analyses. The rest of the patients were clinically followed up and 64 were considered in CS by a consensus between the pulmonologists and rheumatologists. The initial consensus was based on the application of both MAS and HLH criteria; however, among the first few patients, very few met these criteria despite worsening clinical status and elevation of inflammatory markers. Hence, a newly devised consensus was based on (1) worsening respiratory status defined as increased oxygen supplementation required to maintain SpO_2>93% and (2) elevation above threefold the upper normal level of at least two of the following markers: C reactive protein (CRP), ferritin, D-dimer, lactate dehydrogenase (LDH) and cardiac troponin. Patients in this group were retrospectively selected as the basis for the following statistical analyses.

To validate the results, an additional cohort of 258 patients was collected from all the patients admitted to Temple University Hospital from 18 April 2020 to 30 April 2020. Inclusion criteria were the same of the first cohort.

Statistical analyses

A series of univariate logistic regressions were used to assess the association between each laboratory variable and the presence of the CS, with the criterion of the clinical consensus of the medical group indicating the presence of the storm (see previous discussion). The predictors were the laboratory variables, aggregated by using each patient average up to the day when the clinicians made the consensus of CS or the first 7 days of hospitalisation for patients not diagnosed in storm. Due to the presence of missing values, only predictors obtained in at least 300 patients were considered.

Predictors showing a significant odds ratio, at alpha-level 0.05, were then analysed by principal component analysis (PCA) with promax rotation to cluster them in coherent groups. We retained the components (clusters) having eigenvalues larger than 1. Each laboratory variable was associated with the cluster in which it featured the highest factor loading.

Cut-off values for each individual laboratory variable were estimated using a *genetic algorithm*[22] as implemented by Scrucca[23] (for more details, see online supplemental methods). In the algorithm, a population of 500 sets of cut-off values was defined, with mutation probability of 0.1 and crossover probability of 0.8. In each generation, 5% of the sets of cut-off values were selected based on their fitness. The fitness function maximised the geometric mean of the sensitivity and specificity of the classification (confusion table) predicting the (COVID-19 cytokine storm (COVID-CS)) groups obtained with a given set of cut-off values. The stopping rule was set to 200 generations with no improvement in fitness. In order to develop cut-offs that can be feasibly used in the clinic, daily laboratory data were used in the genetic algorithm fitness function. A patient was classified as COVID-CS positive when the criteria were met at least for 1 day. When a laboratory value was not present for a patient 1 day, the most recent available value was used.

To evaluate the stability of the cut-off values, a bootstrap procedure was employed to compute the CI classification statistics (accuracy, sensitivity and specificity). For each statistic, a distribution of bootstrap estimates was created across 5000 bootstrap samples, and the 95% CIs were obtained by setting the 2.5th and 97.5th percentiles of the bootstrap distribution as the interval boundaries. Finally, the criteria and cut-off values were also validated on the second cohort of patients.

Table 1 Demographics and comorbidities in the cohort of patients with COVID-19

Patients with COVID-19	All	Clinical consensus		P value
		No storm	Storm	
Numbers	513	449	64	*<0.001*
%	100	88	12	
Sex (%)				
Females	43	45	33	*<0.001*
Males	57	55	66	
Age (years)	58.3	57.7	62.2	*0.041*
Race/ethnicity (%)				
AA	53	54	53	n.s.
EA	11	11	14	n.s.
Hispanic	23	22	19	n.s.
Other	9	9	9	n.s.
Unknown	4	4	5	n.s.
Comorbidities (%)				
Lung disease	26	24	36	0.077
Hypertension	69	68	72	n.s.
Obesity	52	51	55	n.s.
Heart disease	25	25	25	n.s.
Smoking history	42	43	36	n.s.
Diabetes	48	50	36	0.057

Patients with diagnosis of COVID-19 infection and chest high-resolution CT with ground-glass opacity were divided according to a consensus of clinicians for a diagnosis of cytokine storm. P values were calculated using χ^2 test for frequencies and t-test for age.
Italics indicate significant p values.
AA, African–American; EA, European–American; n.s., not significant at $\alpha \geq 0.05$.

RESULTS

Description of the cohort

In this retrospective study, we investigated 513 patients who presented GGOs by chest HRCT. Ninety-five per cent of the patients were also COVID-19 positive by RT-PCR. Of these 513, 64 patients were eventually determined to be in CS and treated with biologics, such as monoclonal antibodies against IL-6R and recombinant IL-1R antagonist (table 1). Table 1 shows the demographics of the cohort, comparing patients who reached or not a clinical consensus for CS. As previously reported in COVID-19 pneumonia, more patients were male, and the average age was 58.3. Mirroring the population that our hospital serves, most patients were African–American and Hispanic. Frequent comorbidities included hypertension, obesity, diabetes and smoking history. We did not find any statistically significant difference in the distribution of race and comorbidities between the patients in storm or not, while older male patients were slightly more likely to develop CS, suggesting that sex and age, but not race and specific comorbidities, increase the risk of developing CS during COVID-19 infection.

COVID-CS does not meet the 2004 HLH criteria and HScore

To understand the type of CS occurring during COVID-19 infection, we determined the number of patients in our cohort who fulfilled the HLH criteria and had an HScore ≥169 (online supplemental tables S1 and S2)[4 24] using the averages of laboratory tests performed during the first 7 days of hospitalisation. We found that only 10 out of 513 patients fit the 2004 HLH criteria (table 2), and most patients (8/10) did not fulfil the clinical consensus of COVID-19 storm. We also found that 43 out of 513 patients had an HScore of >169, but only 12 also met the

Table 2 HLH, HScore and MAS criteria applied to the COVID-19 cohort

	Clinical consensus storm		H Score	Clinical consensus storm		MAS	Clinical consensus storm	
HLH	No	Yes		No	Yes		No	Yes
No	441	62	No	418	52	No	443	63
Yes	8	2	Yes	31	12	Yes	6	1

For HLH criteria, the specificity was 0.98 and the sensitivity was 0.2. For HScore, the specificity was 0.93 and the sensitivity was 0.28. For MAS, the specificity was 0.98 and the sensitivity was 0.14.
HLH, haemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome.

clinical consensus of COVID-19 storm (table 2). In our analyses of the HLH criteria and HScore, most patients admitted with COVID-19 infection did not have splenomegaly (not shown) nor cytopenias affecting at least two cell lineages in the peripheral blood. On the contrary, they had normal absolute numbers of monocytes and increased numbers of neutrophils. They also had normal or increased levels of fibrinogen, typically low in HLH, and mostly normal triglycerides, which are frequently increased in HLH[4] (online supplemental table S4). All patients with COVID-19 had high levels of serum ferritin. In addition, CRP, which is not included in the HLH 2004 criteria (online supplemental table S1), was also elevated. We could not evaluate natural killer (NK)-cell activity and the level of soluble interleukin-2 receptor (sIL-2R), since the results of these tests were not rapidly available at our medical centre or in most hospitals. Nevertheless, reports of other cohorts of patients with COVID-19 showed sIL-2R levels below those considered in the HLH criteria.[25] The analysis of haemophagocytosis in the bone marrow or in secondary lymphoid organs was deemed unnecessary, considering its invasiveness. Even if the tests that we did not perform were hypothetically positive, the majority of patients did not meet the five out of eight criteria of HLH because the majority fulfilled only two—fever and hyperferritinemia. Therefore, our results suggest that most patients in our cohort who developed a CS did not meet the HLH criteria and the HScore[24] performed poorly as previously suggested (table 2).[12]

COVID-CS does not meet the 2016 MAS criteria

We analysed whether our cohort fulfilled the MAS criteria, reported in online supplemental table S3,[5] and found that only 7/513 did (table 2). Six out of seven of these patients were not clinically found in storm, therefore fulfilling neither the laboratory nor the clinical judgement of MAS. These patients did not fit the MAS criteria due to the uncommon presence of thrombocytopenia, increased levels of fibrinogen and the relatively normal levels of triglycerides in the COVID-19-infected patients (online supplemental table S4).

Criteria to predict the COVID-CS

Since most patients with COVID-19 in CS did not meet the classification criteria of HLH, HScore or MAS, we next followed the strategy depicted in figure 1 and analysed the predictive power of 62 laboratory tests available in our hospital (table 3 and online supplemental table S4). We aimed to find novel criteria to identify patients in CS. In order to reach a predictive power that can be clinically useful to diagnose a COVID-CS, we used the mean values of laboratory results of the first 7

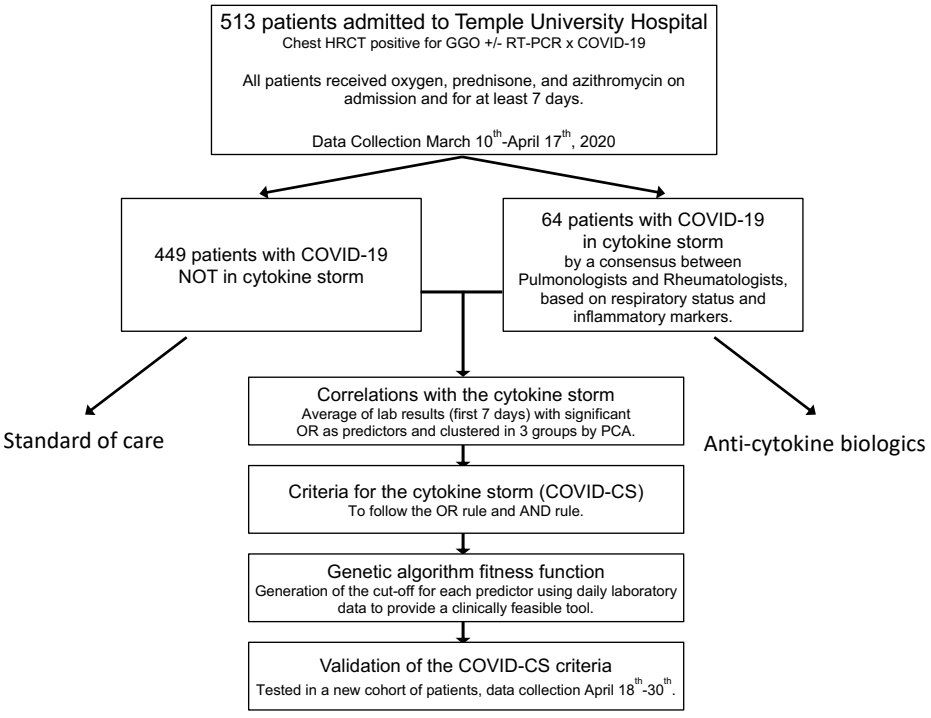

Figure 1 Research strategy. Flowchart of the experimental strategy followed in the generation of the new criteria aimed to recognise the cytokine storm in patients with COVID-19. COVID-CS, COVID-19 cytokine storm; GGO, ground-glass opacity; HRCT, high-resolution CT; PCA, principal component analysis; RT-PCR, reverse transcriptase PCR.

Table 3 Laboratory parameters in the cohort of patients with COVID-19

	Normal range	All	Clinical consensus		OR	P value
			No Storm	Storm		
Albumin	3.2–4.6 g/dL	2.9±0.6	2.9±0.6	2.7±0.5	0.637	*0.001*
ALT	16–61 U/L	45±46	43±37	58±86	1.254	*0.04*
Anion gap	6–16 mmol/L	7.6±3.0	7.8±3.0	7±3.1	0.734	*0.04*
AST	15–37 U/L	54±92	50±80	82±145	1.249	*0.028*
BUN:creatinine ratio	10–20 ratio	18.9±8.3	18.5±8	21±10	1.295	*0.03*
Chloride	101–111 mmol/L	104±5	104±5	106±5	1.316	*0.032*
CRP	0–0.4 mg/dL	7.2±6.4	6.9±6.4	9.1±6.1	1.341	*0.016*
D-dimers	0–500 ng/mL	3,227±11,306	2,396±7,851	8,817±23,356	1.41	*0.002*
LDH	84–246 U/L	323±169	305±153	447±212	1.892	*<0.001*
Lymphocytes Abs	1–4.8 K/mm^3	1.23±2.16	1.28±2.30	0.86±0.41	0.058	*<0.001*
Lymphocytes (%)	20%–40%	18±10	19±11	12±7	0.389	*<0.001*
Neutrophil Abs	1.8–7.8 K/mm^3	6±3.6	5.8±3.6	7.23±3.5	1.4	*0.004*
Potassium	3.5–5.2 mmol/L	4.09±0.5	4.07±0.51	4.23±0.59	1.392	*0.019*
Troponin I	0.045–0.1 ng/mL	0.23±2.29	0.1±0.38	1.07±6.1	2.727	*0.045*

Average and SD of the laboratory parameters collected up to the 24 hours within reaching the clinical consensus of CS or in the first 7 days of hospitalisation in patients with COVID-19 who never reached the clinical consensus of CS. ORs and p values were calculated by logistic regression. Normal range of values is shown for our laboratory as reference.
Abs, absolute numbers; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C reactive protein; CS, cytokine storm; LDH, lactate dehydrogenase.

days of hospitalisation or up to the 24 hours within reaching the clinical consensus of CS. Using the logistic regression, we found that 12 laboratory parameters predict development of CS and by PCA, we determined that these 12 variables could be included in three coherent clusters (table 4). Based on factor analysis, we considered the parameters belonging to the same cluster as alternative indicators (OR rule), with the rationale that parameters of the same cluster highly correlate and may be indicators of the same condition or mechanism. We considered parameters belonging to the different clusters instead as necessary indicators (AND rule) because they represent conditions or mechanisms that should be met. Our analyses highlighted three clusters of laboratory results, and the alteration of one parameter for each cluster predicts the development of COVID-CS (table 4).

Table 4 Predictive criteria for COVID-19 cytokine storm

Entry criteria (must be all met)	Cut-off values
+Signs/symptoms of COVID-19	
±RT-PCR positive for COVID-19	
+GGO by HRCT (or chest X-ray)	
Ferritin	>250 ng/mL
C reactive protein	>4.6 mg/dL
AND (one variable from each cluster)	
Cluster I	
Albumin	<2.8 g/dL
Lymphocytes (%)	<10.2
Neutrophil Abs	>11.4 K/mm^3
Cluster II	
ALT	>60 U/L
AST	>87 U/L
D-dimers	>4,930 ng/mL
LDH	>416 U/L
Troponin I	>1.09 ng/mL
Cluster III	
Anion gap	<6.8 mmol/L
Chloride	>106 mmol/L
Potassium	>4.9 mmol/L
BUN:creatinine ratio	>29 ratio

Criteria are met when patients fulfil all the entry criteria and at least one criterion per each cluster. Cut-off values were calculated using a genetic algorithm.
Abs, absolute numbers; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GGO, ground-glass opacity; HTCT, high-resolution CT; LDH, lactate dehydrogenase; RT-PCR, reverse transcriptase PCR.

The first cluster included decreased levels of albumin and percentage of lymphocytes, along with increased absolute numbers of neutrophils in patients in storm compared with patients who did not develop a storm (tables 3 and 4). The absolute number of lymphocytes formed a separated component and correlated with the first cluster, and we excluded it from the criteria because of its close correlation and redundancy with the percentage of lymphocytes. The second cluster included the increased levels of alanine aminotransaminase (ALT), aspartate aminotransferase (AST), D-dimers, LDH and troponin I. The third cluster included the decreased anion gap and increased levels of chloride, potassium and blood urea nitrogen (BUN):creatinine ratio (tables 3 and 4). These results highlight an important component of tissue damage occurring during the COVID-CS.

In order to develop cut-offs that can be used in clinical practice, we used daily laboratory parameters and estimated the cut-off for each individual laboratory parameter using a genetic algorithm.[22] The predictive requirement for the first cluster consisted of an albumin<2.87 mg/mL OR lymphocytes<10.2%, OR neutrophil absolute number>11.4×10^3/mL. For the second cluster, ALT>60 IU/L, OR AST>87 IU/L, OR D-dimers>4930 ng/mL, OR LDH>416 U/L OR troponin I>1.09 ng/mL were required. For the third cluster, anion gap<6.8 mmol/L, OR chloride>106 mmol/L, OR potassium>4.9 mmol/L OR BUN:creatinine ratio>29 were required (table 4).

Interestingly, ferritin and CRP had the widest ranges and had discriminatory power only if transformed by logarithmic scale. They were therefore added as such in the analyses. Although the performance of their predictive algorithm did not add any power, for clinical reassurance of an ongoing systemic inflammation, we propose to add them to the predictive criteria of COVID-CS (table 4).

Table 5 Validation of the novel criteria of COVID-CS

COVID-CS new criteria					Consensus storm	
	N	%	LoS (days)*	Mortality (%)*	No	Yes
All group						
No	340	66	5.7±6.7	6.6	330	10
Yes	173	34	15.1±13	28.8	119	54
					SP=0.73	SE=0.84
						ACC=0.75
No trials group						
No	308	71.5	5.3±6.7	6.4	300	8
Yes	123	28.5	15.3±13.7	28.1	78	45
					SP=0.79	SE=0.85
						ACC=0.80

The new COVID-CS criteria were applied to the cohort (left) and to the same patients divided according to the clinical consensus of cytokine storm (right). All group includes all the COVID-19 cohort (513, 64 patients who reached and 449 who did not reach the clinical consensus of COVID-19 cytokine storm). No trials group includes 431 patients of the cohort because it excludes 82 patients with COVID-19 who were recruited in clinical trials testing biologic therapies. The new criteria identified patients with significantly greater LoS and mortality.
*P<0.0001.
ACC, accuracy; COVID-CS, COVID-19 cytokine storm; LoS, length of stay; SE, sensitivity; SP, specificity.

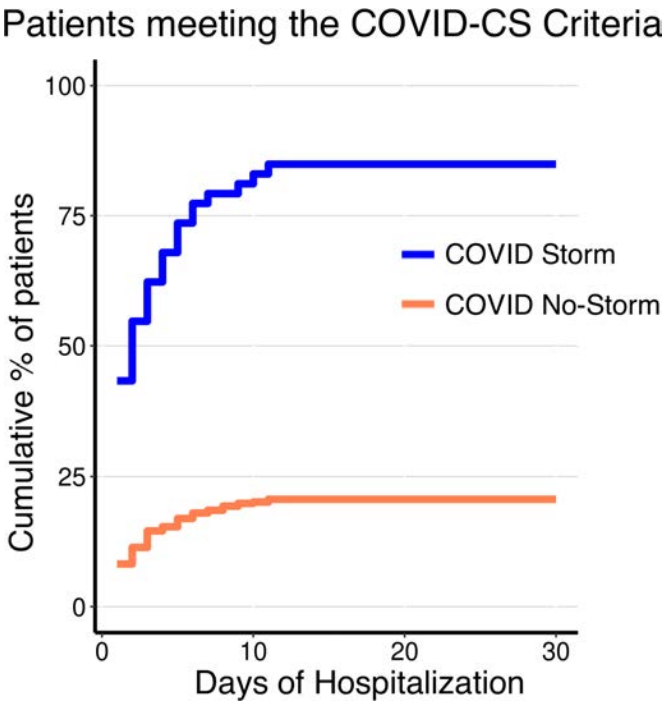

Figure 2 Rapid progression for patients with COVID-19 towards meeting the COVID-CS criteria. The cohort of 431 patients with COVID-19 (no trials) was plotted for the accumulation of the laboratory parameters fulfilling the COVID-CS criteria during hospitalisation. The blue line represents the percentage of patients who received the clinical diagnosis of CS and met the COVID-CS criteria. The orange line represents the percentage of patients who did not receive the clinical diagnosis of CS and met the COVID-CS criteria. COVID-CS, COVID-19 cytokine storm; CS, cytokine storm.

Preliminary validation of the novel criteria of COVID-CS

We validated the ability of the proposed criteria to identify COVID-CS. The upper rows of table 5 show the initial validation where all the patients were included. The criteria classified 34% of the patients as in COVID-CS (173/513). Next, we applied the new criteria to the 64 patients originally considered in CS by clinical consensus, and 84% of them (54/64) were correctly classified as in COVID-CS. The new criteria had a specificity of 0.73 (CI 0.70 to 0.77) and a sensitivity of 0.84 (CI 0.78 to 0.92). We then performed the validation after excluding the 82 patients who were enrolled in clinical trials (table 5, bottom rows). In this subpopulation of 431 patients, the criteria showed an even higher specificity of 0.79 (CI 0.76 to 0.83) and a sensitivity of 0.85 (CI 0.78 to 0.93), suggesting that these criteria have a strong predictive power in our population of patients with COVID-19.

When we analysed the disaggregated laboratory parameters to determine the length of time patients required to meet the criteria of COVID-CS, we found that among the patients with the clinical consensus of CS, 43% met the criteria on hospital admission, and the rest reached the asymptote by 10 days of hospitalisation (figure 2, blue line). Among the patients who did not reach the clinical consensus of CS, 20% met the COVID-CS criteria with a similar timeline (figure 2 orange line). These results suggest an early and rapid progression in those patients bound to develop COVID-CS, as well as the low likelihood of developing the condition 10 or more days into the admission.

COVID-CS criteria identify severely ill patients

To determine whether our criteria could predict clinical severity, we analysed the hospital length of stay (LoS) and mortality. We found that the group of patients who met COVID-CS criteria had a significantly higher LoS (15.1±13 vs 5.7±6.7) and importantly higher mortality (28.8% vs 6.6%) (table 5). For both LoS and mortality, the p value was <0.0001. Excluding the patients in trials yielded similar results.

Markers of inflammation and tissue damage in COVID-CS

We analysed the laboratory results in our cohort of patients now divided as fitting or not the COVID-CS criteria (table 6 and online supplemental figure S1). The COVID-CS group had significantly higher levels of ferritin, CRP and triglycerides, and decreased levels of albumin, all signs of systemic inflammation. Ferritin showed an OR of 14, indicating an important role in COVID-CS. Strong inflammation was confirmed by the level of IL-6, which was elevated in most patients with COVID-19 but significantly higher in COVID-CS (35 vs 96 pg/mL). The white blood cells, and especially neutrophils and monocytes, were significantly increased in the COVID-CS group, suggesting an active role of the innate immunity in the storm. The lymphocytes instead were decreased, with averages half of the normal lower limit, suggesting a functional depletion of the adaptive immunity (table 6 and online supplemental figure S1).

We also found that five markers of tissue damage were significantly higher in patients with COVID-CS than in the rest of the patients with COVID-19. The liver enzymes ALT and AST had levels twice as high, indicative of liver damage, while D-dimers had levels more than six times higher, suggesting endothelial damage. The increase in LDH is a sign of cell death, while the moderately elevated levels of troponin I suggest damage to the cardiovascular system (table 6 and online supplemental figure S1).

Laboratory parameters pertaining to the electrolyte metabolism, namely, chloride, potassium and sodium, the first two predictive of COVID-CS, were still in the normal range, while creatinine, BUN and their ratio were all increased compared

Table 6 Laboratory parameters in the cohort of patients with COVID-19 at Temple University associated with the new criteria of COVID-CS

Parameters	Normal range	All	No COVID-CS	COVID-CS	OR	P value	N
Albumin	3.2–4.6 g/dL	2.9±0.6	3.1±0.6	2.6±0.4	0.292	*<0.001*	495
Ferritin	8–388 ng/mL	947±2,754	502±738	1,701±4,319	14.725	*<0.001*	444
C reactive protein	0–0.4 mg/dL	7.0±6.3	5.8±5.8	9.3±6.5	1.781	*<0.001*	457
Triglycerides	<150 mg/dL	178±205	138±72	234±300	3.120	*<0.001*	330
Interleukin-6	<5 pg/mL	69±126	35±35	96±162	3.799	*<0.001*	75
Lymphocytes (%)	20%–40%	18±10	21±10	11±7	0.217	*<0.001*	509
Monocytes Abs	0–0.8 K/mm^3	0.59±0.28	0.56±0.28	0.63±0.27	1.260	*0.01*	509
Neutrophil Abs	1.8–7.8 K/mm^3	6.00±3.6	4.98±3.1	8.01±3.7	2.602	*<0.001*	509
WBC Abs	4–11 K/mm^3	7.88±4.5	6.83±3.1	9.95±5.8	2.818	*<0.001*	508
ALT	16–61 U/L	45±46	35±25	65±66	2.830	*<0.001*	495
AST	15–37 U/L	53±88	40±76	79±101	2.883	*<0.001*	495
D-dimers	0–500 ng/mL	3,119±10,443	1,017±2,138	6,933±16,648	10.409	*<0.001*	456
LDH	84–246 U/L	323±166	249±87	456±191	10.545	*<0.001*	462
Troponin I	0.045–0.1 ng/mL	0.23±2.29	0.05±0.12	0.55±3.8	438.236	*<0.001*	416
Chloride	101–111 mmol/L	104±5.4	103±4.8	105±6.1	1.627	*<0.001*	509
Potassium	3.5–5.2 mmol/L	4.09±0.5	3.99±0.5	4.29±0.5	1.815	*<0.001*	509
Sodium	136–145 mmol/L	137±4.01	136±3.14	138±5.12	1.607	*<0.001*	509
Creatinine	0.6–1.10 mg/dL	1.89±2.8	1.61±2.5	2.43±3.3	1.317	*0.003*	509
BUN	8–20 mg/dL	27±25	21±19	39±32	2.266	*<0.001*	509
BUN:creatinine ratio	10–20 ratio	18.9±8.4	17.1±6.4	22.6±10.5	2.076	*<0.001*	509

Average and SD of the laboratory parameters collected in the first 7 days of hospitalisation in patients with COVID-19 divided according to the new COVID-CS criteria. ORs and p values were calculated by univariate logistic regression. Normal range of values is shown for our laboratory as reference.
Abs, absolute numbers; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; COVID-CS, COVID-19 cytokine storm; LDH, lactate dehydrogenase; WBC, white blood cell.

with the upper normal limits in patients fitting the criteria of COVID-CS. These results suggest a prerenal imbalance and renal damage (table 6 and online supplemental figure S1). Together, these results highlight systemic tissue damage affecting many organs in the COVID-CS.

Second validation of the COVID-CS criteria

Finally, we further validated the novel criteria by applying them to a second cohort of 258 patients, 128 women and 130 men, with a mean age of 59 years. Out of the 258 patients, 39 (15%) were considered in CS by the same clinical consensus used in the first cohort. In the new cohort, the novel criteria correctly classified 69% of the patients, with a specificity of 0.73 (CI 0.69 to 0.78) and a sensitivity of 0.69 (CI 0.58 to 0.81), indicating that the criteria can be successfully applied to new cohorts. Similar to the first cohort, patients who met the criteria (33%) had significantly higher LoS (15.5±10.1 vs 4.7±3.7, p<0.001) and mortality (33.7% vs 4.2%, p<0.0001) (online supplemental table S5).

DISCUSSION

Our analyses highlight the unique features of COVID-CS. We found that laboratory parameters indicative of a strong proinflammatory status, systemic cell death and multiorgan tissue damage, and prerenal electrolyte imbalance are predictive of this hyperimmune condition. We found clear differences with other CSs, such as MAS, from which COVID-CS is distinguished for the uncommon thrombocytopenia and the increased number of neutrophils, suggestive of an active innate immune system. Other distinct differences were the increased levels of fibrinogen and the relatively normal levels of triglycerides in the COVID-CS, which, together with the low levels of albumin, suggest a different type of inflammation.

Despite the limitations of missing three HLH criteria and one for the HScore, namely, the hemophagocytosis, the NK-cell activity and the sIL-2R, we propose that the lack of cytopenias, the normal levels of fibrinogen and the only mildly elevated levels of triglycerides indicate that the COVID-CS is very different from HLH and the HScore is not useful.[12]

It was recently reported that LDH, CRP and low lymphocytes are associated with higher mortality in patients with COVID-19.[18 26] Our results are in agreement with these studies. Indeed, our COVID-CS criteria identify a group of patients with longer LoS and increased mortality. Therefore, our criteria predict not only the development of the storm but also clinical severity. Both CD4+ and CD8+ T cells were initially reported to be decreased in severe cases of COVID-19[27 28] and more recently were shown to recover during disease resolution.[29] T cells are pivotal in the elimination of viral infected cells.[30] Moreover, it has been shown in other CSs that the excess of cytokines can be due to a deficient elimination of cytokine-producing innate immune cells, such as inflammatory monocytes and macrophages, by CD8+ T cells.[31] Therefore, low lymphocytes as criterion for COVID-CS highlight the role of deficient T-cell functions in COVID-CS pathogenesis, allowing innate immunity overactivation and uncontrolled viral infection.[32]

The increased levels of cell death markers such as liver enzymes, LDH, D-dimers and troponin I indicate that COVID-CS is characterised by significant systemic tissue damage that in different patients may target the liver, the cardiovascular system and the kidney, as suggested by recent autopsy results.[13–16] High levels of D-dimers have been reported in several cohorts of patients with COVID-19 and correlate with increased mortality.[33] The elevated levels of LDH, D-dimers and troponin, especially early on, could also indicate pulmonary immunothrombosis and secondary pulmonary arterial hypertension, both implicated in the devastating lung damage that COVID-19 inflicts.[34]

Therefore, anticoagulant therapy has been recommended in those with high levels,[35] and our therapeutic approach has changed as well. Compared with the initial cohort, the validation cohort received higher and earlier doses of steroids, and a larger percentage received anticoagulants. These changes might explain the lower sensitivity of the criteria in the validation cohort; nevertheless, they remain very valuable as there is not yet a standard to aggressively or conservatively treat patients with COVID-CS around the world.

Acute respiratory distress syndrome (ARDS) is undeniably one of the most lethal manifestations of COVID-19 infection.[36] The abnormal laboratory work in our criteria could be explained by ARDS in which both hypoxia and hyperaemia could drive elevation of LDH, liver enzymes and renal dysfunction with albumin levels as predictor of ARDS.[37 38] Nevertheless, a significant number of immunoprofiling results point to a systemic inflammatory response with the lung at the epicentre.[32 38 39]

There are limitations to our work. First, in the absence of an established definition of COVID-CS in the literature, the clinical 'gold standard' was defined by the clinical judgement of CS itself. Second, the vast majority of our patients received steroids as part of the early standard of care at Temple University.[40] Third, our investigation was conducted in a single centre and with a specific racial/ethnicity composition. These limitations might make our cohort somewhat different from other centres. Future validations with other cohorts from multiple centres and countries will resolve these limits.

The high levels of cell death markers shed light in COVID-CS pathogenesis. Both necroptosis and pyroptosis can occur during viral infections and are mediated by proinflammatory cytokines such as interferon-gamma and IL-1-beta and by inflammasome.[32 41] A recent longitudinal immune analysis revealed a subgroup of patients who eventually died of COVID-19 with a cytokine profile indicative of CS, inflammasome involvement and tissue damage.[32] In this group, the levels of IL-6 were extremely elevated.[32] We also found elevated IL-6 levels in all patients and more in COVID-CS, although not as high as reported by others [32 39] possibly because we tested early during hospitalisation. Together with the high levels of CRP, which is induced by IL-6,[42] as COVID-CS criterion, these findings demonstrate the validity of our criteria in capturing the impending storm. Several clinical trials testing cytokine inhibitors are presently ongoing in patients with COVID-19 and may soon provide evidence for a role of cytokine-mediated cell death in patients with COVID-CS.

In summary, we provide new criteria to diagnose the COVID-CS at an early stage, which predict longer hospitalisation and increased mortality, therefore requiring specific treatments. While the criteria need further validation, they represent a first step toward early diagnosis and intervention in this lethal pandemic.

Author affiliations
[1]Medicine/Rheumatology, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, USA
[2]Department of Psychology, University of Milano-Bicocca, Milan, Italy
[3]Radiology, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, USA
[4]Microbiology and Immunology, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, USA
[5]Pediatrics, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, USA
[6]Medicine/Hematology, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, USA
[7]Thoracic Medicine and Surgery, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, USA

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Collaborators Temple University COVID-19 Research Group: Aaron Mishkin; Abbas Abbas; Abhijit S Pathak; Abhinav Rastogi; Adam Diamond; Aditi Satti; Adria Simon; Ahmed Soliman; Alan Braveman; Albert J Mamary; Aloknath Pandya; Amy Goldberg; Amy Kambo; Andrew Gangemi; Anjali Vaidya; Ann Davison; Anuj Basil; Arthur Lau; Arundathi Jayatilleke; Bakhos, Charles T; Bill Cornwell; Brent Lawrence; Brianna Sanguily; Brittany Corso; Carla Grabianowski; Carly Sedlock; Catherine Myers; Charles Bakhos; Chenna Kesava; Reddy Mandapati; Cherie Erkmen; Chethan Gangireddy; Chih-ru Lin; Christopher T Burks; Claire Raab; Crabbe, Deborah; Crystal Chen; Daniel Edmundowicz; Daniel Sacher; Daniel Salerno; Daniele Simon; David Ambrose; David Ciccolella; Debra Gillman; Dolores Fehrle; Dominic Morano; Donnalynn Bassler; Edmund Cronin; Eduardo Dominguez; Ekam Randhawa; Ekamjeet Randhawa; Eman Hamad; Eneida Male; Erin Narewski; Francis Cordova; Frederic Jaffe; Frederich Kueppers; Fusun Dikengil; Galli, Jonathan; Gangemi, Andrew; Garfield, Jamie; Gayle Jones; Gennaro Calendo; Gerard Criner; Gilbert D'Alonzo; Ginny Marmolejos; Gordon, Matthew; Gregory Millio; Gupta, Rohit; Gustavo Fernandez; Hannah Simborio; Harwood Scott; Heidi Shore-Brown; Hernan Alvarado; Ho-Man Yeung; Ibraheem Yousef; Ifeoma Oriaku; Iris Jung-won Lee; Isaac Whitman; James Brown; Jamie L. Garfield; Janpreet Mokha; Jason Gallagher; Jeffrey Stewart; Jenna Murray; Jessica Tang; Jeyssa Gonzalez; Jichuan Wu; Jiji Thomas; Jim Murrett; Joanna Beros; John M. Travaline; Jolly Varghese; Jordan Senchak; Joseph Lambert; Joseph Ramzy; Joshua Cooper;Jun Song; Junad Chowdhury; Justin Levinson; Kaitlin Kennedy; Karim B Ahmed; Karim Loukmane; Karthik Shenoy; Kathleen Brennan; Keith Johnson; Kevin Carney; Kevin Lu; Kraftin Schreyer; Kristin Criner; Kumaran, Maruti; Lauren Miller; Laurie Jameson; Laurie Johnson; Laurie Kilpatrick; Lawrence Brent; Lii-Yoong Criner; Lily Zhang; Lindsay K Mcgann; Llera A Samuels; Marc Diamond; Margaret Kerper; Maria Vega Sanchez; Mariola Marcinkienwicz; Maritza Pedlar; Mark Aksoy; Mark Weir; Marla R. Wolfson; Marla Wolfson; Marron, Robert; Martin Keane; Massa Zantah; Mathew Zheng; Matthew Delfiner; Matthew Gordon; Maulin Patel; Megan Healy; Melinda Darnell; Melissa Navaro; Meredith A. Brisco-Bacik; Michael Bromberg; Michael Gannon; Michael Jacobs; Mira Mandal; Nanzhou Gou; Narewski, Erin; Nathaniel Marchetti; Nathaniel Xander; Navjot Kaur; Neil Nadpara; Nicole Desai; Nicole Mills; Norihisa Shigemura; Ohoud Rehbini; Oisin O'Corragain; Omar Sheriff; Oneida Arosarena; Osheen Abramian; Paige Stanley; Parag Desai; Parth Rali; Patrick Mulhal; IPravin Patil; Priju Varghese; Puja Dubal; Puja Patel; Rachael Blair; Rajagopalan Rengan; Rami Alashram; Randol Hooper; Rebecca A Armbruster; Regina Sheriden; Robert Marron; Rogers Thomas; Rohit Gupta; Rohit Soans; Roman Petrov; Roman Prosniak; Romulo Fajardo; Ruchi Bhutani; Ryan Townsend; Sabrina Islam; Samantha Pettigrew; Samantha Wallace; Sameep Sehgal; Samuel Krachman; Santosh Dhungana; Sarah Hoang; Sean Duffy; Seema Ran; iShapiro William; Sheila Weaver; Shelu Benny; Sheril George; Shuang Sun; Shubhra Srivastava-Malhotra; Stephanie Brictson; Stephanie Spivack; Stephanie Tittaferrante; Stephanie Yerkes; Stephen Priest; Steve Codella; Steven G Kelsen; Steven Houser; Steven Verga; Sudhir Bolla; Sudhir Kotnala; Sunil Karhadkar; Sylvia Johnson; Tahseen Shariff; Tammy Jacobs; Thomas Hooper; Tom Rogers; Tony S. Reed; Tse-Shuen Ku; Uma Sajjan; Victor Kim; Whitney Cabey; Wissam Chatila; Wuyan Li; Zach Dorey-Stein; Zachariah Dorey-Stein; Zachary D Repanshek.

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ORCID iDs
Roberto Caricchio http://orcid.org/0000-0002-1379-1118
Marcello Gallucci http://orcid.org/0000-0003-3546-0093
Stefania Gallucci http://orcid.org/0000-0003-4737-8003

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Comparative effectiveness of first-line tumour necrosis factor inhibitor versus non-tumour necrosis factor inhibitor biologics and targeted synthetic agents in patients with rheumatoid arthritis: results from a large US registry study

Dimitrios A Pappas ,[1,2] Gregory St John,[3] Carol J Etzel,[2] Stefano Fiore,[4] Taylor Blachley,[2] Toshio Kimura,[5] Rajeshwari Punekar,[6] Kelechi Emeanuru,[2] Jeannie Choi,[6] Susan Boklage,[3] Joel M Kremer[2,7]

Handling editor Josef S Smolen

[1]Division of Rheumatology, Department of Medicine, Columbia University Medical Center, New York, New York, USA
[2]Corrona, LLC, Waltham, Massachusetts, USA
[3]Regeneron Pharmaceuticals, Inc, Tarrytown, New York, USA
[4]R&D, Sanofi, Bridgewater, New Jersey, USA
[5]Medical Analytics, Regeneron Pharmaceuticals Inc, Tarrytown, New York, USA
[6]Sanofi, Bridgewater, New Jersey, USA
[7]Albany Medical College, Albany, New York, USA

Correspondence to
Dr Dimitrios A Pappas, Division of Rheumatology, Department of Medicine, Columbia University Medical Center, New York, NY 10032, USA; dpappas@corrona.org

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ABSTRACT

Objectives This study evaluated the comparative effectiveness of a tumour necrosis factor inhibitor (TNFi) versus a non-TNFi (biological disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs)) as the first-line treatment following conventional synthetic DMARDs, as well as potential modifiers of response, observed in US clinical practice.

Methods Data were from a large US healthcare registry (Consortium of Rheumatology Researchers of North America Rheumatoid Arthritis Registry). The analysis included patients (aged ≥18 years) with a documented diagnosis of rheumatoid arthritis (RA), a valid baseline Clinical Disease Activity Index (CDAI) score of >2.8 and no prior bDMARD or tsDMARD use. Outcomes were captured at 1-year postinitiation of a TNFi (adalimumab, etanercept, certolizumab pegol, golimumab or infliximab) or a non-TNFi (abatacept, tocilizumab, rituximab, anakinra or tofacitinib) and included CDAI, 28-Joint Modified Disease Activity Score, patient-reported outcomes (including the Health Assessment Questionnaire Disability Index, EuroQol-5 Dimension score, sleep, anxiety, morning stiffness and fatigue) and rates of anaemia. Groups were propensity score-matched at baseline to account for potential confounding.

Results There were no statistically significant differences observed between the TNFi and non-TNFi treatment groups for outcomes assessed, except the incidence rate ratio for anaemia, which slightly favoured the TNFi group (19.04 per 100 person-years) versus the non-TNFi group (24.01 per 100 person-years, p=0.03). No potential effect modifiers were found to be statistically significant.

Conclusions The findings of no significant differences in outcomes between first-line TNF versus first-line non-TNF groups support RA guidelines, which recommend individualised care based on clinical judgement and consideration of patient preferences.

Key messages

What is already known about this subject?

- American College of Rheumatology guidelines for the treatment of rheumatoid arthritis (RA) recommend a treat-to-target approach that is guided by disease stage and treatment history.
- However, based on comparisons of tumour necrosis factor inhibitor (TNFi) agents versus non-TNFi agents in head-to-head randomised clinical trials, the optimal sequence of different treatment modalities following conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) is not established.

What does this study add?

- Real-world, comparative evidence to aid clinical decision-making for patients who failed therapy on csDMARDs revealed only limited differences in baseline characteristics and clinical outcomes between adult patients with RA initiating treatment with a TNFi versus a non-TNFi following csDMARDs.

How might this impact on clinical practice?

- The findings support RA guidelines which recommend individualised care based on clinical judgement and consideration of patient preferences.

BACKGROUND

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune condition characterised by joint damage, stiffness and swelling.[1] As the most common inflammatory arthritis in adults, RA affects up to 1.28–1.36 million US adults (2014 estimates).[2 3] In addition to symptom relief, the aim of treatment is normalisation or improvement in physical function, health-related quality of life and social and work capacity. Inhibition of structural damage is the key marker of treatment success, for which disease-modifying antirheumatic drugs (DMARDs) remain the mainstay modality.[4]

American College of Rheumatology guidelines for the treatment of RA recommend a treat-to-target approach that is guided by disease stage and treatment history.[2] Initial modalities for the treatment pathway comprise conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), for example, methotrexate, sulfasalazine, leflunomide

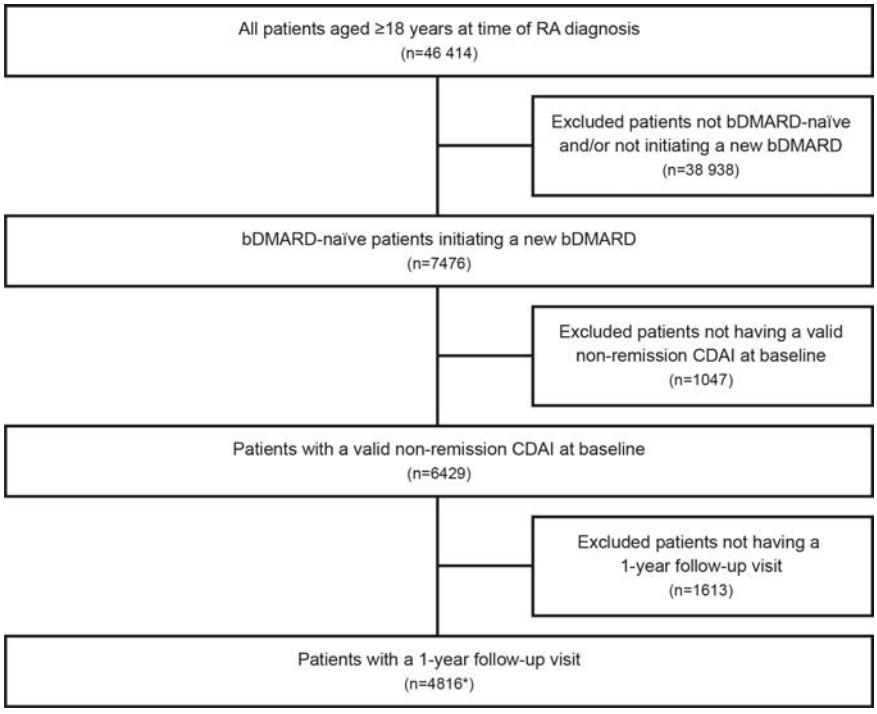

Figure 1 Selection of eligible patients: eligible patients were selected using the 31 January 2018 version of the RA database. *bDMARD initiations include TNFi initiations (n=4186; adalimumab: n=1464, etanercept: n=1322, certolizumab pegol: n=229, golimumab: n=139, infliximab: n=1032) and non-TNFi initiations (n=630; abatacept: n=369, tocilizumab: n=53, rituximab n=94, anakinra: n=14, tofacitinib: n=100), bDMARD, biological disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

and hydroxychloroquine, with the option of concomitant short-term glucocorticoids for disease flares or moderate/high disease activity.[2] For patients with inadequate response or intolerance to csDMARDs, a switch to or an addition of a biologic DMARD (bDMARD) or a targeted synthetic DMARD (tsDMARD; presently only comprising the janus kinase (JAK) inhibitors) is recommended;[2] bDMARD options broadly comprise tumour necrosis factor inhibitor (TNFi) and non-TNFi agents (e.g. T-cell costimulatory inhibitors, anti-B-cell agents and anti-interleukin (IL)-6 receptor monoclonal antibodies.

Table 1 Prepropensity and postpropensity score-matched baseline characteristics

	Prematching			Postmatching		
	TNFi* (n=4186)	Non-TNFi† (n=630)	Standardised difference	TNFi‡ (n=2372)	Non-TNFi§ (n=593)	Standardised difference
Age (years), mean (SD)	56.9 (12.7)	62.7 (13.0)	–0.4476¶	61.0 (12.9)	62.3 (12.8)	–0.1005¶
Female, n (%)	3202 (76.5)	503 (79.8)	–0.0807	1821 (76.8)	473 (79.8)	–0.0726
White, n (%)	3443 (82.7)	511 (81.5)	0.0783	1956 (82.8)	483 (81.9)	0.1025¶
Duration of rheumatoid arthritis (years), mean (SD)	7.1 (8.6)	8.6 (9.7)	–0.1564¶	8.2 (9.3)	8.7 (9.5)	–0.0602
Rheumatoid factor positive, n (%)	1862 (71.1)	240 (69.8)	0.0291	1032 (70.2)	228 (70.4)	–0.0036
Concomitant csDMARD, n (%)	3485 (83.3)	476 (75.6)	0.1912¶	1851 (78.0)	455 (76.7)	0.0312
Prednisone use, n (%)	1312 (31.3)	198 (31.4)	–0.0019	752 (31.7)	185 (31.2)	0.0109
BMI, mean (SD)	30.1 (7.2)	29.6 (7.2)	0.0668	30.0 (7.1)	29.8 (7.3)	0.0377
CDAI score (0–76), mean (SD)	20.4 (13.5)	20.4 (13.2)	–0.0150	19.8 (13.2)	20.1 (13.1)	–0.0256
HAQ score (0–3), mean (SD)	1.0 (0.6)	1.1 (0.6)	–0.0744	1.1 (0.6)	1.1 (0.6)	–0.0036
Comorbidity history, n (%)						
Serious infections	631 (15.1)	101 (16.0)	–0.0264	373 (15.7)	95 (16.0)	–0.0081
Cancer	316 (7.5)	97 (15.4)	–0.2481¶	289 (12.2)	87 (14.7)	–0.0730
Cardiovascular disease	332 (7.9)	69 (11.0)	–0.1035¶	238 (10.0)	64 (10.8)	–0.0248
Anaemia	128 (3.1)	29 (4.6)	–0.0806	84 (3.5)	28 (4.7)	–0.0593

*Adalimumab (n=1464), etanercept (n=1322), certolizumab pegol (n=229), golimumab (n=139) and infliximab (n=1032).
†Abatacept (n=369), tocilizumab (n=53), rituximab (n=94), anakinra (n=14) and tofacitinib (n=100).
‡Adalimumab (n=759), etanercept (n=734), certolizumab pegol (n=155), golimumab (n=87) and infliximab (n=637).
§Abatacept (n=352), tocilizumab (n=49), rituximab (n=88), anakinra (n=11) and tofacitinib (n=93).
¶Standardised difference >0.1 or <–0.1.
BMI, body mass index; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; TNFi, tumour necrosis factor inhibitor.

Presently, the optimal sequence of different treatment modalities following csDMARDs is not established; based on evidence comparing non-TNFi agents versus TNFi agents in head-to-head randomised clinical trials[2]; current guidelines state no definitive preference of TNFi or non-TNFi as first-line bDMARD treatment. Therefore, to aid clinical decision-making for this segment of the RA treatment pathway, the generation of comparative evidence is warranted.

OBJECTIVES

This observational study compared baseline characteristics and important clinical and patient-reported outcomes (PROs) of patients with RA initiating a TNFi versus a non-TNFi as the first-line bDMARD or tsDMARD using data from a large US healthcare registry. Any association between patient characteristics and treatment outcomes (ie, effect modification) was further assessed.

METHODS

Study design

Data were prospectively collected for the period between 1 October 2001 and 31 January 2018 within a large US healthcare registry (Consortium of Rheumatology Researchers of North America (Corrona) RA Registry).[5 6] Adult patients (aged ≥18 years) included in the study had a documented diagnosis of RA and a valid Clinical Disease Activity Index (CDAI) score of >2.8.[7] In addition, patients were to have initiated a first-line bDMARD or tsDMARD: either a TNFi (adalimumab, etanercept, certolizumab pegol, golimumab or infliximab) or non-TNFi (abatacept, tocilizumab, rituximab, anakinra or tofacitinib) during the study period. Patients who did not have a non-remission CDAI score at baseline and a 1-year post initiation follow-up visit were excluded from analysis.

Baseline patient and disease characteristics were captured for each eligible patient, with clinical outcomes and PROs collected at 1 year postinitiation of index treatment. If a visit at 1 year was not available, then a visit within ±3 months of this timepoint was used. For patients discontinuing index treatment prior to the 1-year follow-up, values at discontinuation were used, except for binary outcomes, which were imputed.

The key clinical outcome of interest was CDAI score, which was used to assess (1) achievement of low disease activity (CDAI score of ≤10) among those with moderate or high baseline disease activity at baseline, (2) achievement of remission (CDAI score of ≤2.8) among those with low, moderate or high disease activity at baseline, (3) achievement of minimally important difference in CDAI (defined as an improvement in the CDAI score of ≥2 if the baseline CDAI score was 2.8–10.0, ≥6 if the baseline CDAI score was 10.1–22.0 and ≥11 if the baseline CDAI score was >22).[8] Secondary clinical outcomes included 28-Joint Modified Disease Activity Score (mDAS28),[9] which was used to assess achievement of remission (mDAS28<2.6). The rate of anaemia (defined as haemoglobin levels of <13.2 g/L for men and <11.5 g/L for women) was also of interest due to its association with inflammation associated with RA[10] and exacerbated by some treatments. In the Corrona RA registry, anaemia is captured as a comorbidity or adverse event reported by physicians during the study visits.

PROs captured included the Health Assessment Questionnaire Disability Index (HAQ-DI), EuroQol-5 Dimension (EQ-5D) score,[11] problem with sleep (yes or no), anxiety (yes or no), morning stiffness (presence and duration) and fatigue (visual analogue scale of 0–100).

Analysis

Propensity score matching of baseline characteristics

To account for potential confounding introduced by identified imbalanced covariates, groups were first propensity score-matched (via greedy matching without replacement) prior to statistical comparison. Standardised differences were calculated to identify baseline characteristics that were not balanced to consider for inclusion in propensity score matching. Variables that had |standardised difference|>0.1 were considered imbalanced. Imbalanced covariates with over 10% missing data were then excluded. Matching ratios were considered to maximise the sample size while balancing as many covariates as possible.

Comparison of outcomes

Following propensity score matching, outcomes at 1 year postinitiation were compared between matched TNFi and non-TNFi cohorts. Random effect logistic regression models were used for binary outcomes; random effect linear regression models were used for continuous outcomes; and rate of anaemia was analysed via a random effect Poisson regression model. Models were adjusted by baseline value for clinical outcomes and PROs, concomitant csDMARD use and prednisone use. Random effect regression models were fit with physician random effects to account for correlation of responses for patients nested within physician.

Determination of effect modifiers

To determine any association between baseline characteristics and outcomes observed (ie, effect modification), the following binary covariates that were hypothesised to influence response were selected and examined via multivariable random effect models: gender, age, race, education, smoking status, body mass index (BMI), median systolic blood pressure, history of hypertension, history of diabetes, history of anaemia, work status, private insurance, prior csDMARD use, median duration of RA, median tender joint count, median swollen joint count, median physician global assessment and median patient global assessment. Interaction terms between potential effect modifiers and treatment group were used to identify the estimated effect in each covariate group; a Bonferroni correction was applied when examining tests for statistical significance to account for assessments on multiple outcome measures, and a Bonferroni-corrected alpha level of 0.00019 was considered statistically significant. This correction was imposed due to the high number of tests performed for evaluating potential effect modifiers.

RESULTS

Within the Corrona RA Register, 46 414 patients aged ≥18 years were identified over the study period. Of those, 7476 patients had been initiated with an eligible medication and were bDMARD-naïve and tsDMARD-naïve. A total of 1047 patients did not have a valid non-remission CDAI score at baseline, and 1613 patients did not have a 1-year postinitiation follow-up visit. This resulted in 4816 eligible patients, comprising n=4186 that had been initiated with treatment with a TNFi and n=630 that had been initiated with treatment with a non-TNFi (figure 1).

After consideration of standardised differences, imbalanced covariates that were selected for inclusion in the propensity score matching model included demographic variables (age, sex, insurance type, marital status, smoking status and work status) and clinical variables (BMI, baseline CDAI, duration of disease, American College of Rheumatology functional status,[12]

concomitant csDMARDs cardiovascular and hypertension history, and prior cancer and prednisone use).

The following imbalanced covariates had >10% missing data and were therefore excluded from the propensity score model: diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, patient global assessment, haemoglobin and number of times per week engaged in intense physical activity.

A matching ratio of 1:4 (non-TNFi:TNFi) provided an optimal balance of baseline covariates while preserving the maximal sample size for analyses of outcomes.

After propensity score matching, 2372 and 593 patients remained in the TNFi and non-TNFi groups, respectively.

Baseline characteristics

Prematching, the mean age of the TNFi group was 56.9 years versus 62.7 years for the non-TNFi group (table 1); baseline CDAI was similar between the groups (20.4). Relatively more patients in the TNFi group received concomitant csDMARDs (83.3% vs 75.6%), consistent with the clinical evidence in the guidelines which recommend TNFi in combo with csDMARDs.[2] Postmatching, the groups appeared largely similar in terms of baseline characteristics (table 1); the mean ages were 61.0 and 62.3 years, with 76.8% and 79.8% female patients, and the mean duration of RA was 8.2 and 8.7 years in the TNFi and non-TNFi groups, respectively. Concomitant csDMARD use was also balanced postmatching (78.0% vs 76.7% in the TNFi and non-TNFi groups, respectively).

Outcomes

There were no statistically significant differences observed between the TNFi and non-TNFi treatment groups for binary outcomes, including achievement of low disease activity, achievement of remission (defined according to CDAI and mDAS28), achievement of minimum clinically important difference in CDAI, and problems with sleep and anxiety (figure 2). While the raw proportion of patients with anaemia was not significantly different prematching and postmatching, TNFi initiators had a lower crude incidence rate of anaemia (19.04 cases per 100 person-years) when compared with non-TNFi initiators (24.01 cases per 100 person-years, p=0.03) (figure 3 and table 2, unadjusted test not shown). This relationship persisted in adjusted analyses (adjusted incidence rate ratio=0.79, 95% CI 0.64 to 0.98).

For continuous variables, there were no significant differences observed between the TNFi and non-TNFi treatment groups; these outcomes included changes in CDAI score, HAQ-DI score, EQ-5D score, morning stiffness and fatigue over the 12-month postinitiation period (table 2).

Effect modification

Of the potential effect modifiers examined, none were found to be statistically significant at a Bonferroni-corrected alpha level of 0.00019.

DISCUSSION

The present study, which was based on observations in US clinical practice, revealed only limited differences in baseline

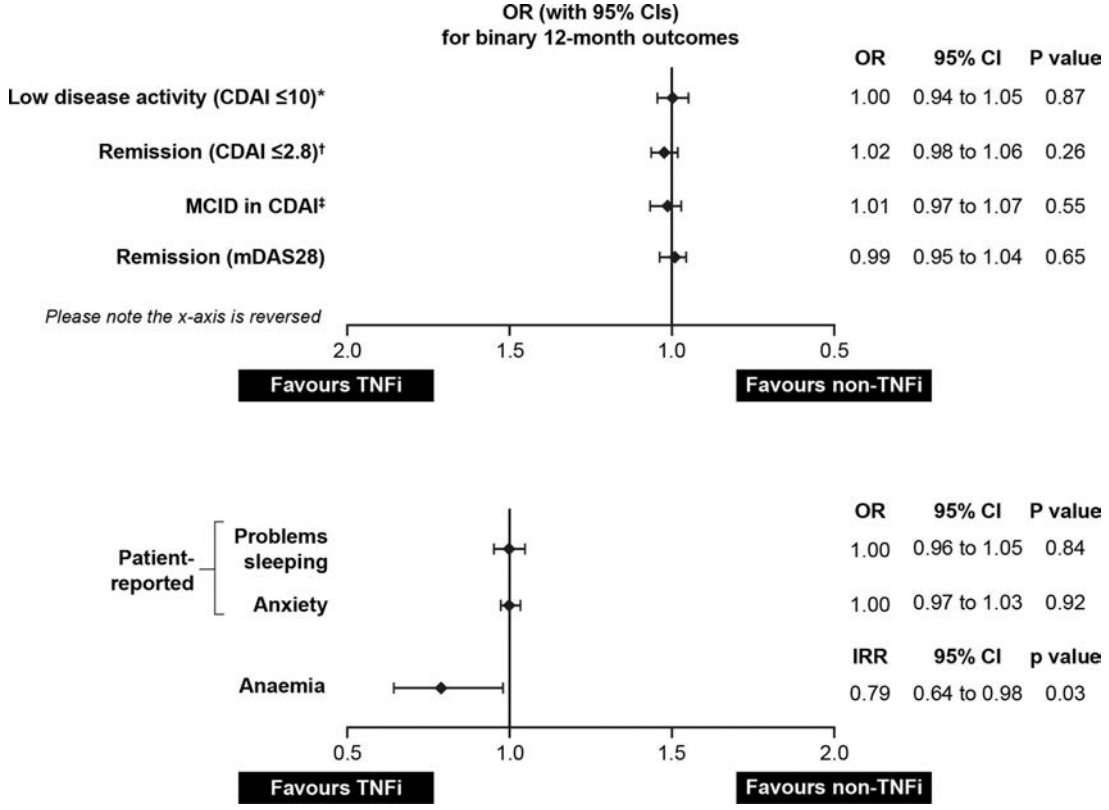

Figure 2 Odds ratio for binary and count outcomes for 12-month period post-TNFi/non-TNFi initiation. *Among those with moderate or high disease activity at baseline. †Among those with low, moderate or high disease activity at baseline. ‡Defined as ≥2 if baseline CDAI score of 2.8–10.0; ≥6 if baseline CDAI score of 10.1–22.0; ≥11 if baseline CDAI score of >22. CDAI, Clinical Disease Activity Index; IRR, incidence rate ratio; MCID, minimum clinically important difference; mDAS28, 28-Joint Modified Disease Activity Score; OR, odds ratio; TNFi, tumour necrosis factor inhibitor.

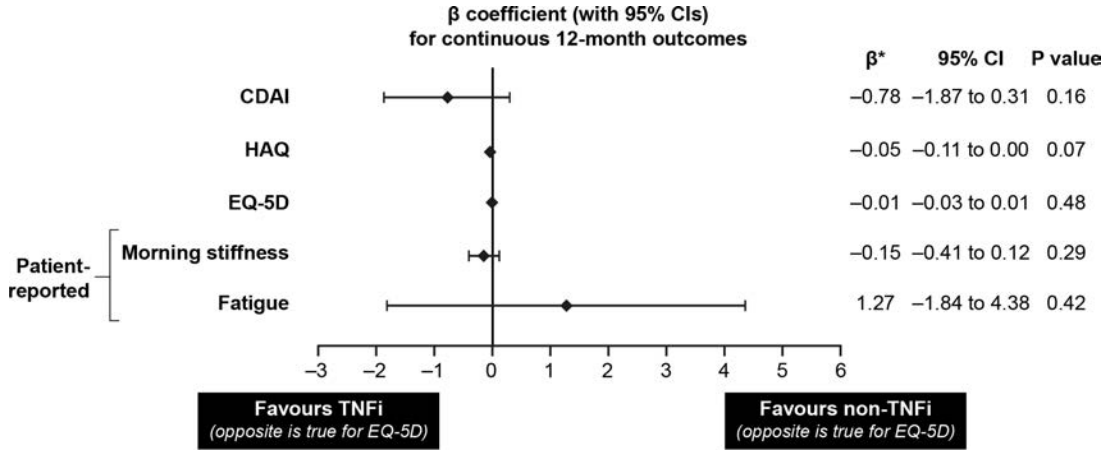

Figure 3 β-coefficients for continuous outcomes for 12-month period post-TNFi/non-TNFi initiation. *Change in continuous outcomes is defined as the outcome value at 1-year follow-up minus the outcome value at baseline. CDAI, Clinical Disease Activity Index; EQ-5D, EuroQol-5 Dimension; HAQ; Health Assessment Questionnaire; TNFi, tumour necrosis factor inhibitor.

characteristics and clinical outcomes (but not PROs) between adult patients with RA initiating treatment with a TNFi versus a non-TNFi. At baseline, the relatively larger proportion of patients in the TNFi group receiving concomitant csDMARDs supports clinical evidence in guidelines which recommend TNFi in combination with csDMARDs.[2] Insofar as a lower crude incidence rate of anaemia was found for TNFi initiators versus the non-TNFi initiators, these results can be viewed as being largely inconclusive for two reasons. First, the disproportionately low usage of IL-6 and JAK inhibitor treatments in this study was insufficient to uphold the observed results. Second, a large body of evidence supports the association between IL-6 inhibitors and increased haemoglobin levels[13–15] in patients with RA, with JAK inhibitors having a neutral association.[16–18] Supplementary to these findings was the observation that no patient characteristics impacted treatment effect on RA outcomes; however, longer

Table 2 Overall comparison of outcomes by treatment group

	TNFi initiators	Non-TNFi initiators	TNFi versus non-TNFi*	
All patients	2372	593	–	–
Binary outcomes	**Response rate n/N (%)**	**Response rate n/N (%)**	**Adjusted OR (95% CI)**	**P value†**
Achievement of low disease activity (CDAI score of ≤10)‡	597/1498 (39.9)	154/370 (41.6)	1.00 (0.94 to 1.05)	0.87
Achievement of remission based on CDAI (≤2.8)§	363/2066 (17.6)	82/504 (16.3)	1.02 (0.98 to 1.06)	0.26
Achievement of MID in CDAI¶	940/2066 (45.5)	227/504 (45.0)	1.01 (0.97 to 1.07)	0.55
Achievement of remission based on mDAS28	449/1835 (24.5)	118/447 (26.4)	0.99 (0.95 to 1.04)	0.65
Patient-reported problem with sleep**	451/1937 (23.3)	114/496 (23.0)	1.00 (0.96 to 1.05)	0.84
Patient-reported anxiety**	239/1937 (12.3)	62/496 (12.5)	1.00 (0.97 to 1.03)	0.92
Patient-reported problem with sleep††	588/2363 (24.9)	136/591 (23.0)	1.02 (0.98 to 1.06)	0.35
Patient-reported anxiety††	308/2363 (13.0%)	73/591 (12.4%)	1.01 (0.98 to 1.04)	0.70
Count outcomes	**Incidence rate (per 100 person-years)**	**Incidence rate (per 100 person-years)**	**Adjusted IRR (95% CI)**	**P value**
Anaemia	19.04	24.01	0.79 (0.64 to 0.98)	0.03
Continuous outcomes	**N, mean±SD**	**N, mean±SD**	**Adjusted β coefficient (95% CI)‡‡**	**P value**
Change in CDAI	2065, −6.8±14.0	504, −6.5±13.8	−0.78 (−1.87 to 0.31)	0.16
Change in HAQ	1732, −0.1±0.6	373, −0.1±0.5	−0.05 (−0.11 to 0.00)	0.07
Change in EQ-5D	1097, 0.0±0.2	357, 0.0±0.2	−0.01 (−0.03 to 0.01)	0.48
Change in patient-reported morning stiffness (hours per day)	1599, −0.3±2.5	396, −0.2±2.9	−0.15 (−0.41 to 0.12)	0.29
Change in patient-reported fatigue	1119, −4.7±30.1	363, −6.3±26.2	1.27 (−1.84 to 4.38)	0.42

*Estimates from multivariable models.
†The reported p values are associated with the adjusted ORs.
‡Among those with moderate or high disease activity at baseline.
§Among those with low, moderate or high disease activity at baseline.
¶Defined as ≥2 if baseline CDAI score=2.8–10; ≥6 if baseline CDAI score=10.1–22; ≥11 if baseline CDAI score>22.
**Imputed as missing if patients switched to another biologic before 1-month follow-up.
††Imputed with the last observation on drug.
‡‡Change in continuous outcomes is defined as the outcome value at 1-year follow-up minus the outcome value at baseline.
CDAI, Clinical Disease Activity Index; EQ-5D, EuroQol-5 Dimension; HAQ, Health Assessment Questionnaire; IRR, incidence rate ratio; mDAS28, 28-Joint Modified Disease Activity Score; MID, minimum important difference; TNFi, tumour necrosis factor inhibitor.

follow-up may indicate if the post-treatment observation is clinically meaningful.

The findings from this real-world study are consistent with findings from systematic reviews of data from randomised controlled trials, which have also shown no significant differences between TNFi and non-TNFi treatments in patients initiated with a bDMARD.[19 20] While in monotherapy separate comparative effectiveness studies[21] revealed clinical superiority of IL-6 inhibitors to TNFs, this was not observable in the present study, given the disproportionately low IL-6 use in the non-TNFi cohort. Similarly, other real-world[22] and trial-based comparative effectiveness[19 23 24] studies in RA patients with previous anti-TNF exposure real-world evidence point to similar outcomes between TNFi cycling and switching to a non-TNFi.

This study is the first to attempt to address the dearth of comparative evidence, in terms of baseline patient characteristics and treatment outcomes, of TNFi and non-TNFi treatment approaches to address the inadequacy of initial csDMARD therapy for RA in a real-world setting. Robust statistical comparison methodologies were applied to cohorts, with differences corrected for at baseline.

The Corrona RA Registry is the largest disease-based registry in the USA, with broad geographical presence in rural and urban areas. It comprises data from academic and private practices and includes patients from all socioeconomic and racial strata. In addition, external validation of the registry data to different data sources lend further support to the generalisability and credibility of the data.[25] Considering this and the long time frame over which the study was conducted, findings can be considered largely representative of the RA patient population in the USA as has been demonstrated in a study comparing the characteristics of Corrona patients with a Medicare database.[25] However, as with any retrospective observational study, the level of generalisability is difficult to quantify.

To minimise the potential for channelling bias of different kinds of patients into the treatment regimen arms, a propensity-matching approach was used; as such, it is possible that some residual channelling existed that was not detected. Results may have been influenced by the effect of pooling index treatments into two categories: TNFi and non-TNFi. While mechanisms of action are similar for all TNFi included, distinct mechanisms of action exist within the non-TNFi group. It is possible that individual comparisons would wield different outcomes and effect modifiers, though the extent to which this would alter conclusions cannot be quantified without further investigation.

The study provides an indication of the comparative effectiveness of TNFi versus non-TNFi as the first-line treatment after csDMARD for adult patients with RA, addressing the limited evidence and resulting lack of directive provided in current treatment guidelines. Although new entrants to the bDMARD treatment market are not reflected in the current data, it can be reasonably expected that findings would have been similar to the current and historical real world, in addition to the trial-based evidence in the literature. Further investigation into the comparative effects of individual TNFi and non-TNFi treatments is warranted, as well as investigation of the comparative effects of individual TNFi after failure of one or more prior TNFi.

CONCLUSIONS

In this large US registry study, patients showed similar improvements in clinical outcomes and PROs after 1 year of treatment regardless of whether initiated with a TNFi or a non-TNFi. The findings of no significant differences in outcomes between first-line TNF and first-line non-TNF groups support RA guidelines which recommend individualised care based on clinical judgement and consideration of patient preferences.[2]

Correction notice This article has been corrected since it published Online First. Figure 2 has been corrected.

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

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ORCID iD

Dimitrios A Pappas http://orcid.org/0000-0001-8338-027X

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CLINICAL SCIENCE

Axial involvement in patients with early peripheral spondyloarthritis: a prospective MRI study of sacroiliac joints and spine

Thomas Renson ,[1,2] Philippe Carron ,[1,2] Ann-Sophie De Craemer,[1,2] Liselotte Deroo,[1,2] Manouk de Hooge ,[1,2] Simon Krabbe ,[3,4] Lennart Jans,[5] Min Chen,[5] Mikkel Østergaard ,[3,4] Filip E Van den Bosch,[1,2] Dirk Elewaut [1,2]

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[1]Internal Medicine and Pediatrics, Ghent University Faculty of Medicine and Health Sciences, Ghent, Belgium
[2]VIB-UGent Center for Inflammation Research, Ghent, Belgium
[3]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, Denmark
[4]Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[5]Radiology, Ghent University Faculty of Medicine and Health Sciences, Ghent, Belgium

Correspondence to
Dr Thomas Renson, Internal Medicine and Pediatrics, Ghent University Faculty of Medicine and Health Sciences, Ghent 9000, Belgium; thomas.renson@ugent.be

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ABSTRACT

Objectives To assess axial involvement on MRI in early peripheral spondyloarthritis (pSpA) and to evaluate whether axial inflammation predicts relapse on treatment withdrawal.

Methods Fifty-six patients with early, active, newly diagnosed pSpA underwent MRI of the sacroiliac joints (SIJs) and spine prior to golimumab initiation. At sustained clinical remission of pSpA, treatment was withdrawn and a second MRI was performed. Bone marrow oedema (BME) was scored by three readers according to the Spondyloarthritis Research Consortium of Canada (SPARCC) method. Scores were compared with an axial spondyloarthritis cohort (Belgian Arthritis and Spondylitis cohort). Structural lesions were assessed using a similar method. Furthermore, fulfilment of the Assessment of Spondyloarthritis International Society (ASAS) definition of a positive MRI for sacroiliitis was assessed. Spinal images were evaluated for BME and structural lesions using the Canada-Denmark MRI spine scoring system by two readers.

Results Thirty-six per cent showed SIJ BME at baseline, all fulfilling the ASAS definition of sacroiliitis. No association with back pain was found. Twenty-one per cent displayed SIJ structural lesions. Spinal BME was limited: the median inflammation scores were low and no patients had ≥5 inflammatory corner lesions. On clinical remission, a significant decrease in SIJ SPARCC scores was detected. On clinical remission, no significant differences in SIJ SPARCC scores were noted between patients relapsing and those maintaining remission after treatment discontinuation.

Conclusion In patients with early pSpA, a surprisingly high prevalence of sacroiliitis on MRI was observed; SPARCC scores decreased significantly on tumour necrosis factor inhibition. Residual inflammation on MRI was not predictive of relapse of peripheral manifestations. No relevant inflammatory spinal involvement was detected. Collectively, our findings suggest a higher inflammatory burden in patients with early pSpA than anticipated.

Key messages

What is already known about this subject?

- Limited, heterogeneous data exist on axial involvement in psoriatic arthritis, whereas no prospective MRI studies have evaluated axial involvement in non-psoriatic peripheral spondyloarthritis (pSpA).

What does this study add?

- This is the first study on axial involvement on MRI in patients with very early pSpA.
- A strikingly high prevalence of sacroiliitis (36%) was observed at baseline, not associated with back pain.
- By contrast, spinal inflammatory and structural MRI scores were low.
- Sacroiliac joint Spondyloarthritis Research Consortium of Canada scores decreased significantly on tumour necrosis factor inhibition.
- Residual sacroiliitis at sustained clinical remission of pSpA was not predictive of relapse of peripheral manifestations.

How might this impact on clinical practice or future developments?

- Our findings indicate a much broader inflammatory burden than clinically suspected, with important overlap between axial and peripheral spondyloarthritis phenotypes.
- Future research may shed new light on the added value of screening for subclinical sacroiliitis, including structural lesions, in patients with a suspicion of pSpA.

INTRODUCTION

Spondyloarthritis (SpA) refers to a disease concept that is characterised by chronic inflammation of the axial and peripheral joints or entheses, often associated with extra-articular manifestations such as psoriasis of the skin and nails, inflammatory bowel disease and acute anterior uveitis.[1] In clinical practice, SpA is typically divided into axial spondyloarthritis (axSpA), that is, involvement of the sacroiliac joints (SIJs) and/or spine, and peripheral spondyloarthritis (pSpA), that is, involvement of the joints and entheses of the extremities. Until now, no studies have evaluated the presence of axial involvement in patients with pSpA in a standardised, prospective way. There are limited data available on axial involvement in psoriatic arthritis (PsA), generally regarded as a subset of the SpA concept.[1–4] At present, the Assessment of Spondyloarthritis

International Society (ASAS) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis are developing a consensus definition of axial involvement in PsA, currently an unmet need. The frequency of axial involvement in PsA is 25%–75% depending on the applied method of evaluation (clinical signs and symptoms, conventional radiography) and symptom duration (early or long-standing disease).[5–7] Up to one-third of patients with PsA display asymptomatic sacroiliitis on conventional radiography,[8–10] and in 2%–5% of patients spondylitis is even the sole musculoskeletal manifestation of PsA.[7 11 12] Unfortunately, MRI data on axial involvement, considered the gold standard to detect active sacroiliitis, in PsA are limited,[13–16] while to our knowledge no studies have been performed in non-psoriatic pSpA. Our goal was therefore to assess axial involvement on MRI of both SIJs and spine in patients with early pSpA, including patients with PsA and non-psoriatic pSpA. Furthermore, we determined whether axial inflammation could act as a predictive factor of relapse of peripheral manifestations after tumour necrosis factor inhibition (TNFi) treatment withdrawal.

METHODS

Study subjects

The Clinical Remission in Peripheral Spondyloarthritis (CRESPA) study was a single-centre, double-blind, placebo-controlled trial with TNFi (golimumab) in patients newly diagnosed with very early pSpA (defined as a symptom duration of less than 12 weeks).[17 18] In order to investigate if an early induction treatment with TNFi would allow drug-free remission, medication was withdrawn if patients reached a status of sustained clinical remission, defined as the absence of arthritis, enthesitis and dactylitis at two major consecutive study visits with a 12-week interval. Subsequently, these patients were prospectively followed to assess the possibility of maintaining drug-free remission or to detect clinical relapse of peripheral manifestations. The study design and first results have been extensively described.[17 18] Patients who fulfilled the Classification for Psoriatic Arthritis (CASPAR) criteria were classified as PsA.[19] To match the SIJ Spondyloarthritis Research Consortium of Canada (SPARCC) scores of CRESPA subjects with those of patients with active axSpA, data from the Belgian Inflammatory Arthritis and Spondylitis (Be-GIANT) cohort, a Belgian nationwide observational registry of patients with newly diagnosed SpA, were used.[20–22] All included patients fulfilled the ASAS classification criteria for axSpA and/or pSpA and were TNFi-naïve prior to inclusion. SPARCC scores of 61 patients younger than 45 years old, newly diagnosed with axSpA, with a positive MRI for sacroiliitis and classified as axSpA according to the ASAS criteria were retained for this analysis.

Magnetic resonance imaging

Participants underwent an MRI of the SIJs and full spine at baseline and at the moment of sustained clinical remission of the peripheral manifestations when treatment was withdrawn. The MRI at timepoint of remission was used to detect significant differences between patients relapsing and those in ongoing drug-free remission. Images were obtained on a 1.5 T MRI unit (Avanto, Siemens Healthineers, Erlangen, Germany). Sequences included 3 mm T1-weighted and short tau inversion recovery (STIR) images of the spine, 3 mm semicoronal T1-weighted turbo spin echo and STIR images of the pelvis. SIJ MRI in Be-GIANT patients was performed using the same MRI device with the same settings and sequences. Images were paired per subject and readers were blinded to timepoint and demographics/clinical characteristics. Images of the pelvis were evaluated for SIJ bone marrow oedema (BME) and structural lesions (sclerosis, fat metaplasia, erosions, (partial) ankylosis), as defined by the ASAS MRI working group, by three trained and calibrated readers (TR, MdH, MC).[23] BME was scored using the SPARCC method, with a maximum score of 72.[24] Furthermore, fulfilment of the ASAS definition of a positive MRI for sacroiliitis was assessed, defined as ≥2 BME lesions on one slice or ≥1 lesion on two consecutive slices and lesions highly suggestive of SpA.[25] Structural lesions were scored using a similar method as for BME[26–29]: six slices, divided into four quadrants, were scored, representing the cartilaginous part of the joint. Per slice, each quadrant was scored for erosions, fat metaplasia, sclerosis and (partial) ankylosis. Individual reader scores were combined, and for further analyses lesions detected by two out of three readers were reported. A consensus score of two out of three readers was used for dichotomous outputs. Spinal images were evaluated independently by two trained and calibrated readers (SK, MØ) for BME, erosions, fat metaplasia and new bone formation, using the Canada-Denmark (CANDEN) MRI spine scoring system.[30] The maximum CANDEN MRI spine scores are 614 for inflammation, 510 for fat, 208 for erosions and 460 for new bone formation. Scores for inflammation, fat, erosion and new bone formation at levels with disc degeneration were excluded from calculation of patient-level sum scores. Levels at T12/L1 to L5/S1 were considered to have disc degeneration if judged as having loss of ≥50% of normally expected disc height, Pfirrmann grade IV ('no clear distinction between annulus and nucleus') or Pfirrmann grade V ('collapsed disc space'). Levels at C2/C3 to T11/T12 were considered to have disc degeneration if scored as having loss of ≥50% of normally expected disc height or Pfirrmann grade V ('collapsed disc space'). To allow comparison with previously developed cut-offs for the number of MRI spine corner inflammatory and structural lesions aiming at high specificity for spondylitis,[27 31] including the ASAS definition of a positive MRI for spondylitis, the presence of at least one anterior or anterolateral corner inflammatory lesion at the same vertebral edge was counted as involvement of one corner, and similarly the presence of at least one posterior or posterolateral corner inflammatory lesion at the same vertebral edge was counted as involvement of one corner, while non-corner lesions in the vertebral bodies and lesions in the posterior elements were not counted. Average scores of both readers were calculated and used for further analyses.

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics V.25. Descriptive statistics were used to analyse the demographics, clinical characteristics and MRI lesions. The significance of SPARCC score differences between timepoints was calculated by the Wilcoxon signed-rank test. The Chi-square test was used to evaluate the differences in proportions of PsA patients versus non-psoriatic pSpA patients having axial involvement. The Mann-Whitney U test was used to check the differences in MRI lesions in the relapse versus drug-free remission group. P values ≤0.05 were considered statistically significant.

RESULTS

Study subjects

The baseline demographics and clinical characteristics of the CRESPA participants have been published previously and are summarised in table 1, next to the included Be-GIANT subjects.[17] Out of 60 CRESPA patients, 56 (93%) underwent an MRI of the

Table 1 Baseline demographics and disease characteristics

	CRESPA total group	CRESPA MRI group	Be-GIANT
Number of participants, n	60	56	61
Age, years, mean±SD	39.7±13.4	39.0±13.2	31.6±6.8
Male gender, n (%)	39 (65)	35 (63)	30 (49)
HLA-B27 positive, n (%)	33 (55)	30 (54)	43 (71)
History of inflammatory back pain (ASAS), n (%)	7 (10)	4 (7)	52 (85)
Visual Analogue Scale back pain, median (IQR)	1 (0–4)	1 (0–4)	4 (2–6)
Symptom duration, mean±SD Arthritis (CRESPA group, in weeks) Axial symptoms (Be-GIANT group, in months)	5.0±2.4	7.1±4.1	52.8±63.4
78 tender joint count, median (IQR)	4 (3–8)	4.5 (3–9)	0 (0–2)
76 swollen joint count, median (IQR)	4 (2–5)	4 (2–6)	0 (0–0)
Swollen joint count ≥5, n (%)	14 (23)	13 (23)	1 (2)
Psoriasis (past/present), n (%)	23 (38)	22 (39)	7 (11)
Anterior uveitis (past/present), n (%)	1 (2)	1 (2)	9 (15)
Inflammatory bowel disease (past/present), n (%)	1 (2)	1 (2)	4 (7)
Elevated CRP (≥5 mg/L) at baseline, n (%)	39 (65)	37 (66)	27 (44)
CRP, median (mg/L) (IQR)	13 (4–36)	13 (4–36)	4 (2–11)
ESR, median (mm/hour) (IQR)	23 (10–44)	22 (8–42)	8 (4–18)

ASAS, Assessment of Spondyloarthritis International Society; Be-GIANT, Belgian Inflammatory Arthritis and Spondylitis; CRESPA, Clinical Remission in Peripheral Spondyloarthritis; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leukocyte antigen B27.

spine and SIJs at baseline. Forty-nine (82%) patients reached a state of sustained clinical remission, whereof only four patients treated with placebo. Forty-five (92%) patients underwent a second MRI of the spine and SIJs at sustained clinical remission. Of these, 20 (44%) relapsed after treatment discontinuation. Out of 56 subjects, 23 (41%) fulfilled the CASPAR criteria and were classified as patients with PsA.

Axial involvement on MRI in early pSpA

Baseline MRI findings

An overview of the detected sacroiliac and spinal MRI lesions is shown in table 2. Examples of axial involvement on MRI in patients with pSpA are shown in figure 1. A high prevalence of SIJ involvement was observed: 20 (36%) patients displayed BME on SIJ MRI at baseline, all fulfilling the ASAS definition of a positive MRI for sacroiliitis. The median SPARCC score among those with a positive MRI for sacroiliitis was 6. Six (11%) patients displayed deep BME lesions, and in nine (16%) patients intense BME lesions were observed. In figure 2, SPARCC scores of CRESPA patients with a positive MRI were matched with those of 61 patients with active axSpA from the Be-GIANT cohort. CRESPA patients with BME on MRI of the SIJs show a similar distribution and range of scores compared with the Be-GIANT subjects (Be-GIANT group: median SPARCC score 7, IQR 4–12). Importantly, structural lesions also commonly occurred in the CRESPA cohort (12 patients, 21%). Erosions were the most frequent structural lesions of the SIJs (16% of patients). Applying the proposed cut-off values by de Hooge *et al*[27] with high diagnostic specificity for axSpA, in five (9%) patients erosions were observed in three or more quadrants, and four (7%) patients showed fat metaplasia in three or more quadrants. Two (4%) patients had partial ankylosis of the SIJs.

Table 2 Inflammatory and structural lesions on MRI at baseline and after reaching sustained clinical remission

	Baseline (n=56)			Remission (n=45)		
	Patients, n (%)	Median* (IQR)	Range* (min–max)	Patients, n (%)	Median* (IQR)	Range* (min–max)
Sacroiliac joints†						
ASAS definition of sacroiliitis	20 (36)	–	–	13 (29)	–	–
SPARCC score (72) ≥1	20 (36)	6 (2–15.5)	1–21	16 (36)	4 (2–6)	1–7
Deep BME (12)	6 (11)	2 (1–4.3)	1–5	0 (0)	–	–
Intense BME (12)	9 (16)	2 (1–3)	1–5	4 (9)	1 (1–1.8)	1–2
Sclerosis (48)	2 (4)	1 (1–1)	1–1	1 (2)	1 (–)	–
Erosions (48)	9 (16)	3 (1.5–5)	1–12	8 (18)	4.5 (1.3–8.3)	1–17
Fat metaplasia (48)	5 (9)	6 (3–16.5)	1–19	4 (9)	8.5 (3–12.5)	2–13
Partial ankylosis (48)	2 (4)	5 (–)	2–8	2 (4)	4 (4–4)	4–4
Ankylosis (48)	0 (0)	–	–	0 (0)	–	–
Spine						
Inflammation score (614)‡	20 (36)	1 (0.5–3)	0.5–10	18 (40)	1 (0.9–3.4)	0.5–10.5
ASAS definition of spondylitis	1 (2)	–	–	4 (9)	–	–
≥5 corner inflammatory lesions	0 (0)	–	–	2 (4)	–	–
Erosion score (208)‡	6 (11)	1.3 (0.5–1.6)	0.5–2.0	4 (9)	1.3 (0.6–1.5)	0.5–1.5
Fat score (510)‡	18 (32)	1.5 (0.5–4.5)	0.5–20	14 (31)	1.5 (0.5–4.6)	0.5–19
≥5 fat lesions	4 (7)	–	–	3 (7)	–	–
New bone formation score (460)‡	10 (18)	4.5 (1–5.3)	1–14	8 (18)	4 (1.5–5.8)	1–14

*Median scores and ranges in patients displaying these particular lesions.
†Maximum scores are indicated between brackets.
‡CANDEN spine scores for inflammation, erosions, fat metaplasia and new bone formation.
ASAS, Assessment of Spondyloarthritis International Society; BME, bone marrow oedema; CANDEN, Canada-Denmark; SPARCC, Spondyloarthritis Research Consortium of Canada.

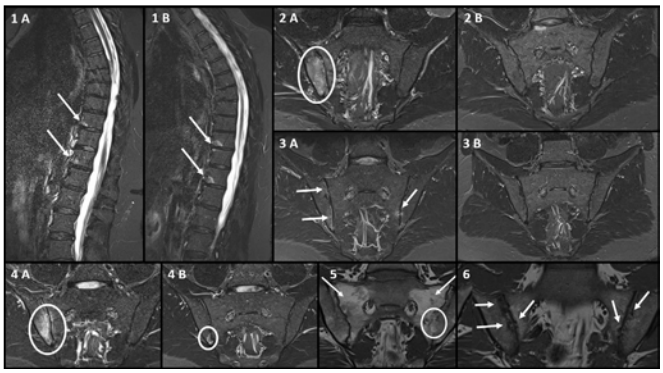

Figure 1 Examples of axial involvement on MRI in early peripheral spondyloarthritis. (1A) Baseline STIR images of a 52-year-old woman displaying spinal bone marrow oedema (corner lesions; indicated by arrows); (1B) STIR images at timepoint of sustained clinical remission of the peripheral manifestations: no decrease on treatment with golimumab (corner lesions indicated by arrows). (2A) Severe iliac bone marrow oedema (indicated by circle) on baseline STIR images in a 28-year-old man; (2B) complete resolution of bone marrow oedema at sustained clinical remission of peripheral spondyloarthritis. (3A) Bilateral sacroiliac bone marrow oedema (indicated by arrows) on STIR images at baseline in a 37-year-old man; (3B) complete resolution of the sacroiliac bone marrow oedema at sustained clinical remission of peripheral spondyloarthritis. (4A) Severe sacroiliac joint bone marrow oedema (indicated by circle) on baseline STIR images in a 29-year-old man; (4B) residual bone marrow oedema (indicated by circle) on remission MRI. (5) Extensive fat metaplasia (indicated by arrows) and partial ankylosis (indicated by circle) on baseline T1 images in a 39-year-old man. (6) Bilateral sacroiliac joint erosions (indicated by arrows) on baseline T1 images in a 37-year-old man. STIR, short tau inversion recovery.

Importantly, we observed no significant differences between patients with PsA and non-psoriatic pSpA (online supplemental table 1).

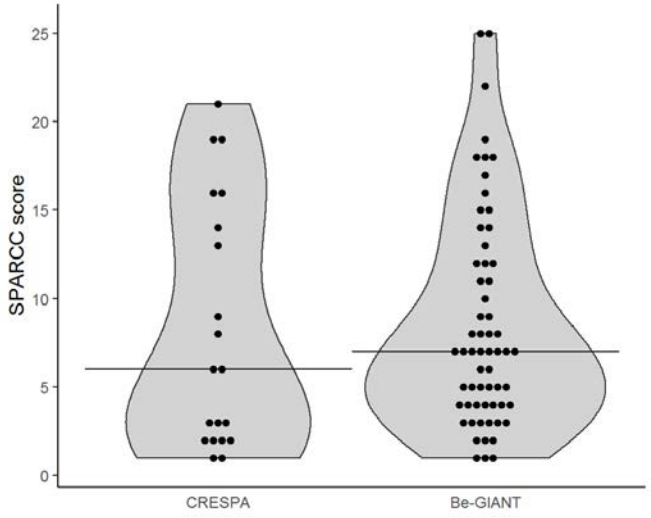

Figure 2 Violin plot displaying sacroiliac joint SPARCC scores of 20 CRESPA patients with sacroiliac joint bone marrow oedema, matched with SPARCC scores of 61 patients with active, newly diagnosed axSpA from the Be-GIANT cohort, an observational registry for prospective follow-up of patients with spondyloarthritis. Be-GIANT, Belgian Inflammatory Arthritis and Spondylitis; CRESPA, Clinical Remission in Peripheral Spondyloarthritis; SPARCC, Spondyloarthritis Research Consortium of Canada.

Contrary to SIJs, spinal BME appeared much less prominent. Even though 20 (36%) patients displayed some degree of spinal BME at baseline, the median inflammation scores were very low (table 2). One patient had a positive MRI for spondylitis according to the ASAS definition. Fat metaplasia was the most observed structural abnormality of the spine at baseline (32%), but similarly as spinal BME, median scores were low. Applying the proposed cut-off values by de Hooge *et al*,[27] no patients had ≥5 corner inflammatory lesions, whereas four (7%) patients displayed ≥5 spinal fat lesions. No obvious differences were noted between PsA and non-psoriatic pSpA, with the exception of a higher proportion of patients with non-psoriatic pSpA with a CANDEN MRI spine inflammation score >0 compared with patients with PsA (online supplemental table 1), although the median values suggest this difference is marginal. There were no differences regarding structural spine involvement between both patient groups.

In addition, the link between sacroiliitis and back pain was evaluated. Only four patients reported ever having an episode of inflammatory back pain (IBP). However, back pain was never a predominant symptom and therefore not the reason for consultation. Only one patient with IBP had an SIJ SPARCC score >0 (SPARCC score=2). Furthermore, no differences in visual analogue scores for back pain in patients with sacroiliitis versus no sacroiliitis were detected (p=0.60).

Remission MRI findings

In subjects with SIJ BME at baseline, SPARCC scores dropped significantly by TNFi on reaching sustained clinical remission (mean 8.9 vs 3.7, p=0.041). Whereas nine (16%) patients had a baseline SPARCC >6, only one patient had a SPARCC score >6 at remission. In contrast, no significant decrease in the CANDEN MRI spine inflammation scores (mean 1.7 vs 1.9, p=0.91) was observed. Patients with pSpA in sustained clinical remission still displayed BME on MRI of the SIJs and spine in 16 (36%) and 18 (40%) patients, respectively, with 13 subjects continuing to fulfil the MRI definition for sacroiliitis and 2 subjects displaying ≥5 corner inflammatory spine lesions at sustained clinical remission (table 2). Nonetheless, one of the latter received placebo and was never treated with TNFi. In addition, scores for SIJ and spinal BME at clinical remission were low. None of the patients showed deep BME lesions on remission MRI of the SIJs, whereas four (9%) patients displayed residual intense BME. No significant differences in the degree of sacroiliitis were found between patients relapsing after treatment discontinuation and those maintaining drug-free remission (mean SPARCC 1.7 vs 1.2, respectively; p=0.51).

DISCUSSION

This is the first study to examine axial involvement in very early pSpA. We found a remarkably high prevalence of axial inflammation on MRI at baseline, since one-third of the patients fulfilled the ASAS definition of sacroiliitis, which appeared to be unrelated to the presence of back pain. By contrast, spinal inflammatory and structural MRI scores were overall very low and no patients had baseline spinal involvement when using a cut-off of at least five inflammatory lesions. A significant decrease in SIJ SPARCC scores was observed after TNFi with overall limited residual inflammation. The presence of sacroiliitis at sustained clinical remission did not predict relapse of pSpA, suggesting that clinical significance of these residual lesions was minimal.

Little data are available on axial involvement in pSpA as most studies are performed in patients with PsA. Notwithstanding,

several issues arise when looking in depth into these previously published data. First, isolated spondylitis is rare among patients with PsA, occurring in less than 5% of patients. Consequently, there is no uniform definition of PsA with solitary axial involvement and no classification criteria exist to date.[32 33] Although axial involvement in PsA can be indistinguishable from axial disease in ankylosing spondylitis (AS), it may have some distinct features, such as a lower prevalence of human leukocyte antigen (HLA-) B27, less axial symptoms, lower Bath AS Metrology Index, less symmetric sacroiliac inflammation and more cervical involvement.[34 35] This raises the question whether axial PsA and AS (with or without psoriasis) represent different clinical presentations of the same disease, or alternatively whether they are two separate diseases with overlapping features. Second, in the existing literature, axial involvement was mainly assessed clinically and/or by conventional radiography. This is problematic, since patients with axial PsA have less IBP than patients with AS.[5 6 10 32 34 36 37] Also, spondylitis without sacroiliitis may occur more frequently in axial PsA, but there is less formation of syndesmophytes.[37 38] Finally, the prevalence of axial involvement in PsA depends on disease duration, with axial inflammation mainly occurring in later disease stages.[11 39] Few MRI studies prospectively evaluated the occurrence of axial inflammation in PsA, irrespective of axial symptoms.[14–16] However, there are currently no data reported on early pSpA. The present report is therefore the first prospective study to analyse axial involvement on MRI in patients with early pSpA, including PsA. We observed a surprisingly high prevalence of inflammatory lesions at the SIJs, with a median SPARCC score of 6 among those displaying SIJ BME. This is significant and likely to be clinically relevant, in view of comparable scores in active non-radiographic axSpA cohorts. Hence, the mean SPARCC score was 4.9 in the total study population of the ABILITY-1 trial, a phase III trial of adalimumab in active non-radiographic axSpA.[40] Furthermore, among those patients with active inflammation on MRI, we reported a median SPARCC score of 7 in the Be-GIANT subjects included in this study. Importantly, a relatively high number of deep BME lesions and structural lesions were also observed, which are less often seen in controls.[41 42] Especially deep BME lesions seem to yield a high specificity for sacroiliitis in the context of SpA.[28 41] In our study, the disappearance of deep BME lesions on TNFi strengthens this statement. Furthermore, Carron *et al* underscored this assumption by showing a very good agreement between deep BME on MRI and clear tracer uptake on immunoscintigraphy with radiolabelled certolizumab pegol in patients with axSpA.[43] SPARCC scores were found to diminish significantly on TNFi. Nonetheless, in some patients sacroiliitis persisted despite treatment with TNFi. This is not uncommon and in line with existing literature in view of the residual mean SPARCC of 4.6 after 16 weeks of golimumab treatment in patients with active non-radiographic axSpA.[44] Similar findings were observed on etanercept treatment.[45] Our findings underscore that the baseline SIJ lesions reflect an important degree of axial involvement, already occurring in an early stage of pSpA. Our study supports the existence of a unifying SpA disease concept, as sacroiliitis in early pSpA is more prevalent than anticipated.[1 2 4 46] Therefore, in contrast to psoriasis patients without arthritis,[47] screening for subclinical sacroiliitis may be of interest in pSpA patients with active arthritis.

Although spinal BME lesions were observed in 36% of patients with pSpA at baseline, inflammation scores were very low. Only one patient had a positive baseline MRI for spondylitis according to the ASAS definition and no patients displayed ≥5 corner inflammatory lesions. Among those with spinal BME, the median CANDEN MRI spine inflammation score was 1 in the present study compared with 5 in an axSpA population.[30] In addition, no significant improvement was observed on TNFi. Therefore, these findings suggest that the presence of spinal inflammation in patients with early pSpA may not be clinically relevant and may rather reflect some aspecific findings commonly occurring in healthy controls. In line with this, two MRI studies reported a high prevalence of spinal inflammatory lesions and fat metaplasia in a non-SpA population.[27 48] Therefore, a uniform, widely accepted and thoroughly validated definition of a positive MRI of the spine is currently an unmet need.[27 48]

Collectively, our findings indicate the existence of an important degree of SIJ inflammation in an early stage of pSpA. By contrast, spinal inflammation overall was limited. Importantly, we did not find a link between the presence of sacroiliitis and back pain. Furthermore, no major differences between PsA and non-psoriatic pSpA were found, suggesting that at least at this early stage much more commonalities exist between these entities. A major strength of the present study is the prospective longitudinal acquisition of spine and SIJ MRI in patients with very early pSpA, both at baseline and at timepoint of sustained clinical remission of the peripheral manifestations. A limitation of our study was the lack of MRIs in patients not achieving clinical remission. In conclusion, this is the first study to evaluate axial involvement in patients with early pSpA. Our findings indicate a much broader inflammatory burden than clinically suspected, as subclinical sacroiliitis is especially common in early pSpA. These results corroborate the unifying concept of SpA with important overlap between axial and pSpA phenotypes.

Twitter Philippe Carron @PhilippeCarron

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ORCID iDs
Thomas Renson http://orcid.org/0000-0002-5503-000X
Philippe Carron http://orcid.org/0000-0001-9254-6171
Manouk de Hooge http://orcid.org/0000-0002-0652-9808
Simon Krabbe http://orcid.org/0000-0002-2877-1582
Mikkel Østergaard http://orcid.org/0000-0003-3690-467X
Dirk Elewaut http://orcid.org/0000-0002-7468-974X

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TRANSLATIONAL SCIENCE

Molecular pathways in patients with systemic lupus erythematosus revealed by gene-centred DNA sequencing

Johanna K Sandling ,[1] Pascal Pucholt ,[1] Lina Hultin Rosenberg,[2] Fabiana H G Farias,[2,3] Sergey V Kozyrev,[2] Maija-Leena Eloranta,[1] Andrei Alexsson,[1] Matteo Bianchi,[2] Leonid Padyukov,[4] Christine Bengtsson,[5] Roland Jonsson,[6] Roald Omdal,[6,7] Benedicte A Lie,[8] Laura Massarenti,[9] Rudi Steffensen,[10] Marianne A Jakobsen,[11] Søren T Lillevang,[11] on behalf of the ImmunoArray Development Consortium and DISSECT consortium, Karoline Lerang,[12] Øyvind Molberg,[12,13] Anne Voss,[14] Anne Troldborg,[15,16] Søren Jacobsen,[17,18] Ann-Christine Syvänen,[19] Andreas Jönsen,[20] Iva Gunnarsson,[4] Elisabet Svenungsson ,[4] Solbritt Rantapää-Dahlqvist,[5] Anders A Bengtsson,[20] Christopher Sjöwall ,[21] Dag Leonard,[1] Kerstin Lindblad-Toh,[2,22] Lars Rönnblom [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Johanna K Sandling and Professor Lars Rönnblom, Department of Medical Sciences, Rheumatology, Rudbeck laboratory C11, Uppsala University, Uppsala 75185, Sweden;
johanna.sandling@medsci.uu.se,
Lars.Ronnblom@medsci.uu.se

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ABSTRACT

Objectives Systemic lupus erythematosus (SLE) is an autoimmune disease with extensive heterogeneity in disease presentation between patients, which is likely due to an underlying molecular diversity. Here, we aimed at elucidating the genetic aetiology of SLE from the immunity pathway level to the single variant level, and stratify patients with SLE into distinguishable molecular subgroups, which could inform treatment choices in SLE.

Methods We undertook a pathway-centred approach, using sequencing of immunological pathway genes. Altogether 1832 candidate genes were analysed in 958 Swedish patients with SLE and 1026 healthy individuals. Aggregate and single variant association testing was performed, and we generated pathway polygenic risk scores (PRS).

Results We identified two main independent pathways involved in SLE susceptibility: T lymphocyte differentiation and innate immunity, characterised by HLA and interferon, respectively. Pathway PRS defined pathways in individual patients, who on average were positive for seven pathways. We found that SLE organ damage was more pronounced in patients positive for the T or B cell receptor signalling pathways. Further, pathway PRS-based clustering allowed stratification of patients into four groups with different risk score profiles. Studying sets of genes with priors for involvement in SLE, we observed an aggregate common variant contribution to SLE at genes previously reported for monogenic SLE as well as at interferonopathy genes.

Conclusions Our results show that pathway risk scores have the potential to stratify patients with SLE beyond clinical manifestations into molecular subsets, which may have implications for clinical follow-up and therapy selection.

Key messages

What is already known about this subject?

- The clinical heterogeneity in systemic lupus erythematosus (SLE) is likely due to an underlying molecular diversity that could have implications for therapy.
- In recent years, gene expression, autoantibody profiles and cytokine levels have been used to identify groups of patients with SLE with distinct molecular disease mechanisms.

What does this study add?

- We have presented a novel strategy to genetically stratify SLE patients according to involved molecular pathways.
- Using genetic information to stratify patients would have the advantages of providing stable molecular markers for early classification.

How might this impact on clinical practice or future developments?

- Our results show that pathway risk scores have the potential to stratify SLE patients beyond clinical manifestations into molecular subsets, which may have implications for clinical follow-up and therapy selection.

INTRODUCTION

Systemic lupus erythematosus (SLE) is characterised by the production of autoantibodies targeting nucleic acids and associated proteins, immune complex formation and inflammation in multiple organs. There is a wide spectrum of clinical manifestations in SLE and extensive heterogeneity in disease presentation between patients; in addition, the treatment response is often unpredictable.[1] The pathogenesis of SLE has partially been clarified during the last years, and important features are increased expression of type I interferon (IFN) regulated genes, defects in the apoptotic process and activated autoreactive B cells.[1 2] The reasons

behind these abnormalities are both environmental and genetic, and today around 100 SLE susceptibility loci have been identified.[3 4] Monogenic forms of SLE exist, but for a majority of patients the environment and the cumulative number of susceptibility alleles will influence the risk of developing the disease.[4 5]

To date, the contribution of rare genetic variants and the impact of regulatory variants have not been widely explored in SLE. DNA sequencing has the potential to discover novel SLE associated variants not captured by genotyping arrays. Due to the high cost, whole genome sequencing studies (WGS) in SLE have so far mainly focused on families or smaller samples, as have exome sequencing studies (WES).[6–9] Today it is feasible to perform targeted sequencing in larger cohorts; however, the number of such studies focusing on SLE is still limited.[10] Additionally, association analysis for rare variants discovered through sequencing is hampered by low statistical power. Aggregating variants on the gene level or by molecular pathway information is one approach to increase power and gain biological insight from rare variants.[11]

The clinical heterogeneity in SLE is likely due to an underlying molecular diversity that could have implications for therapy. In recent years this has started to be addressed, mainly using gene expression, autoantibody profiles and cytokines to identify groups of patients with SLE with distinct molecular disease mechanisms.[12–14] Using genetic information to stratify patients would have the advantage of providing stable molecular markers for early classification.

Here, we performed targeted sequencing of regulatory and coding regions in a Swedish SLE case–control cohort. We aimed at elucidating the genetic aetiology of SLE from the immunity pathway level to the single variant level, and stratify patients with SLE into molecular subgroups. Altogether around 9% of all genes in the human genome were analysed based on their role in immune-mediated diseases. Gene regions were extended to include promoters and other potentially regulatory elements based on mammalian conservation.[15]

METHODS

For full details on methods see online supplemental methods.

Subjects and DNA samples

The Swedish SLE cohorts included patients recruited at five rheumatology clinics and the controls were healthy blood donors and population controls. The quality-controlled dataset comprised 958 patients with SLE and 1026 control individuals. Patients with SLE fulfilled at least four of the classification criteria for SLE as defined by the American College of Rheumatology (ACR).[16 17] Clinical characteristics of the patients are available in online supplemental tables S1A and B.

Targeted DNA sequencing analysis

Targeted DNA sequencing was performed in the Swedish SLE case–control cohorts. A SeqCap EZ Choice XL sequence capture panel was designed, libraries were prepared as described elsewhere[18] and sequenced on an Illumina HiSeq 2500. An overview of the variant discovery and quality control steps can be found in online supplemental figure S1. Study subjects falling outside of the European subpopulation of the Human Genome Diversity Project (HGDP) reference set were excluded (online supplemental figure S7).[19] The quality-controlled dataset contained 287 354 single-nucleotide variants (SNVs) and covered 1832 of the targeted gene regions.

Genetic association analyses

Several variant sets were generated for aggregate association testing: (1) 1832 individual gene variant sets; (2) 35 pathway variant sets based on the Kyoto Encyclopaedia of Genes and Genomes (KEGG)[20] ; (3) five literature review gene sets: the type I interferon pathway,[21] interferonopathy genes,[22 23] SLE Genome-Wide Association Study (GWAS) genes,[3 4] the complement subset of KEGG hsa04610 and genes causing monogenic SLE or lupus-like disease.[24] Aggregate association testing was performed using Sequence Kernel Association Optimal Test (SKAT-O) or GenePy.[25 26] Single variant association analyses were performed in PLINK. SLE case-only variants were identified by removing all SNVs present in our Swedish control dataset, the SweGen project or the Genome Aggregation Database European non-Finnish controls.[27 28]

Risk scores and cluster analysis

Cumulative pathway SLE polygenic risk scores (pathway PRSs) were assigned to each individual based on SNVs associated with SLE at nominal significance. For each independent SNV the natural logarithm of the OR for SLE susceptibility was multiplied by the number of minor alleles in each individual. The sum of all products of all genes in each of the 35 KEGG pathways for each patient was defined as the individual pathway PRS. Hierarchical cluster analysis of pathway PRSs was used to identify groups of patients with SLE.

Replication study and meta-analysis

Replication genotyping in individuals from Norway and Denmark was performed using the MassARRAY system. The Swedish SLE case–control study was expanded to include an additional 1000 control individuals.[27] The Scandinavian meta-analysis included 1794 patients with SLE and 3241 control individuals.

RESULTS

We performed a DNA sequencing study in SLE to study immunity pathways, an overview of analyses can be found in online supplemental figure S2.

T lymphocyte differentiation and innate immunity pathways are associated with SLE

The sequencing data analysis focused on 1832 genes with relevance for immune-mediated diseases. These genes mainly belong to 35 molecular signalling pathways as defined by the KEGG database (online supplemental table S2).[20] Using an aggregate test for all variants in the genes belonging to each pathway, we found that 21 of the tested pathways were associated with SLE (false discovery rate (FDR) <0.05, table 1 and online supplemental table S3). The most significantly associated pathways included T helper cell differentiation pathways, with Th1 and Th2 cell differentiation as the top result ($FDR_{Th1\text{-}2}=2.2\times10^{-9}$; $FDR_{Th17}=1.5\times10^{-8}$), followed by antigen processing and presentation ($FDR=3.1\times10^{-9}$).

We next explored a sequential elimination strategy to identify independent pathway associations. First, removing all Th1 and Th2 pathway genes in the pathway aggregate association test resulted in the antigen processing and presentation pathway as the top result ($FDR=4.8\times10^{-6}$). Second, antigen processing and presentation as well as Th1 and Th2 pathway genes were removed, which resulted in Complement and coagulation cascades as the top result (FDR=0.0091). Third, also genes in this pathway were removed, and the janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway became the

Table 1 SLE case–control pathway based aggregate association analysis

Pathway	Genes in pathway	Genes in test	SNVs in test	P value*	FDR†
Th1 and Th2 cell differentiation (hsa04658)	92	78	14362	6.3E-11	2.2E-09
Antigen processing and presentation (hsa04612)	77	40	8017	1.8E-10	3.1E-09
Hematopoietic cell lineage (hsa04640)	97	71	13013	3.8E-10	4.5E-09
Th17 cell differentiation (hsa04659)	107	96	19347	1.7E-09	1.5E-08
Intestinal immune network for IgA production (hsa04672)	49	39	7909	3.4E-08	2.4E-07
Natural killer cell-mediated cytotoxicity (hsa04650)	131	100	15821	4.7E-06	2.8E-05
TNF signalling pathway (hsa04668)	112	88	12639	1.9E-05	9.4E-05
JAK-STAT signalling pathway (hsa04630)	162	133	18003	7.4E-05	0.00032
RIG-I-like receptor signalling pathway (hsa04622)	70	63	8459	0.00021	0.00080
NOD-like receptor signalling pathway (hsa04621)	178	109	15729	0.00031	0.0011
Complement and coagulation cascades (hsa04610)	79	50	7112	0.00041	0.0013
Toll-like receptor signalling pathway (hsa04620)	104	96	12178	0.00080	0.0022
Cytokine-cytokine receptor interaction (hsa04060)	294	221	26771	0.00083	0.0022
C-type lectin receptor signalling pathway (hsa04625)	104	75	12986	0.0020	0.0050
IL-17 signalling pathway (hsa04657)	93	68	9358	0.0043	0.0100
Fc epsilon RI signalling pathway (hsa04664)	68	51	8514	0.0052	0.011
Viral protein interaction with cytokine and receptor (hsa04061)	100	75	8435	0.0062	0.013
NF-kappa B signalling pathway (hsa04064)	102	88	14349	0.0078	0.015
Osteoclast differentiation (hsa04380)	128	101	18602	0.013	0.023
T cell receptor signalling pathway (hsa04660)	103	85	14268	0.014	0.025
Cytosolic DNA-sensing pathway (hsa04623)	63	40	4993	0.015	0.025

Pathways with FDR <0.05 in the association analysis including all genes are presented.
*SKAT-O SLE case-control association p value.
†SKAT-O SLE case–control association FDR.
FDR, false discovery rate; IL-17, interleukin 17; NF, nuclear factor; NOD, nucleotide-binding oligomerisation domain; RIG, retinoic acid-inducible gene; SKAT-O, sequence kernel association optimal test; SLE, systemic lupus erythematosus; SNV, single-nucleotide polymorphism; TNF, tumour necrosis factor.

top result (FDR=0.014). Lastly, when removing genes in all these four pathways no significant pathways remained. Thus, our data point to two main routes with genetic evidence of association to SLE: T cell differentiation and innate immunity.

To identify the genes that underlie the association signals in the T-cell differentiation, antigen processing and presentation, Complement and coagulation and JAK-STAT pathways, gene-based association testing was performed (figure 1). The top association for the JAK-STAT pathway originated from the IFN kappa (IFNK) gene region. SLE-associated genes in the T cell differentiation and antigen processing and presentation pathways were dominated by genes in the HLA region, and for the complement and coagulation cascade pathway, complement genes located in the HLA region were highly significantly associated with SLE.

Pathway PRS define subsets of patients with SLE

Having identified pathways with genetic association with SLE, we hypothesised that different patients with SLE could have distinct pathways affected. We constructed pathway PRS for each individual and each of the pathways, by combining the burden of common SLE associated alleles from our sequencing data. Individuals with a pathway PRS higher than that observed for the 97.5th percentile of control individuals were classified as positive for that pathway (online supplemental figure S3). The largest proportion of positive SLE patients was observed for the Cytokine-cytokine receptor interaction pathway (41%, figure 2A, and online supplemental table S4). For the Th1 and Th2 cell differentiation, antigen processing and presentation, Complement and coagulation cascades and JAK-STAT signalling pathways 18%, 16%, 21% and 29% of patients with SLE were positive, respectively. On average each SLE patient tested positive for the pathway PRS for seven pathways (figure 2B). As we had previously observed that a high SLE genetic risk score was associated with organ damage in SLE, we investigated whether this could be observed for specific pathways.[5] We found that the SLE International Collaborating Clinics Damage Index was significantly higher in the SLE patients positive for the T cell or B cell receptor signalling pathways (figure 3A,B). No other pathways were associated with clinical manifestations of SLE or survival.

We then performed a hierarchical cluster analysis on the pathway PRSs in SLE, to identify groups of patients with similar molecular aetiology. Four clusters of patients were identified (figure 4). The pathway with the most significant difference in PRS between clusters was the antigen processing and presentation pathway, followed by Th17 cell differentiation (online supplemental figure S4). Next, we investigated whether the molecular stratification of patients with SLE also mirrored differences in clinical presentation between groups. We found that the presence of autoantibodies against Sjögren's syndrome-related antigens SSA and/or SSB was more common among patients in clusters 3 and 4 (figure 3C). We did not observe any significant difference in other clinical features, including survival, between the four patient clusters.

Common variants contribute risk at monogenic risk loci in SLE

We then focused our analysis on gene-sets with prior evidence for involvement in SLE, but which were not defined in KEGG, to investigate the impact of both rare and common variants for these groups of genes. We found that interferon system, interferonopathy, SLE GWAS, complement system and monogenic SLE and lupus-like disease genes in aggregate were associated with SLE when analysing variants of all minor allele frequencies (MAF) (table 2 and online supplemental table S5). Only the

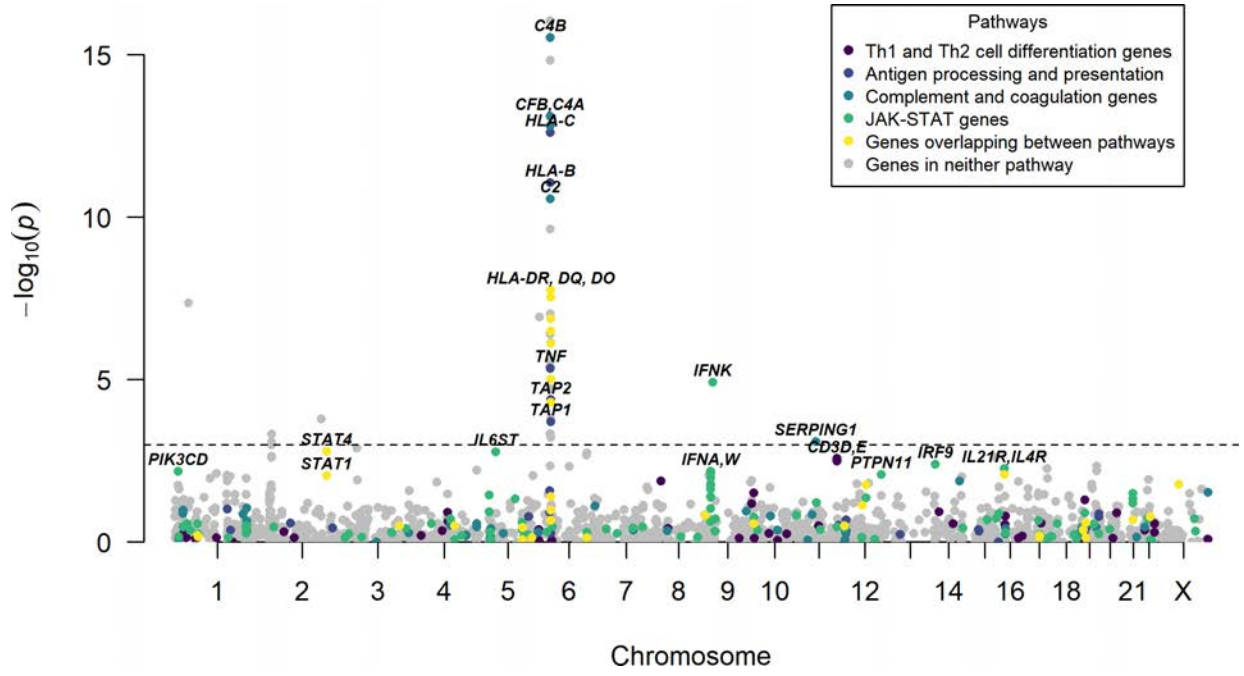

Figure 1 Results of SLE case–control gene-based association analyses. P values for association plotted against chromosomal location, where each point represents a gene region. The line indicates a false discovery rate of 5%. The y-axis has been cut at $p=1\times10^{-15}$. Genes belonging to the T-cell differentiation (Th1 and Th2), antigen processing and presentation, complement and coagulation or JAK-STAT signalling pathways are highlighted, and their most significant genes or gene regions are indicated by name. IFNK, interferon kappa; IL21, interleukin 21; SLE, systemic lupus erythematosus.

monogenic SLE and lupus-like disease gene-set was significantly associated with SLE when separately analysing the rarer variant (MAF <0.01) contribution (table 2). There was a clear common variant (MAF >0.05) contribution to associations for the interferonopathy, SLE GWAS, complement system and monogenic SLE and lupus-like disease gene-sets (table 2).

Potentially novel SLE risk loci

Next, we asked whether we could detect novel SLE risk loci, regardless of pathway or gene-set membership. Two potentially novel gene regions passed a Bonferroni corrected threshold in the gene-based SLE case–control association analyses: *PABPC4* ($p=4.3\times10^{-8}$) and *IFNK* ($p=1.2\times10^{-5}$, online supplemental figure 5A, tables S6 and S7). In single variant association analyses, we observed SNV associations at three potentially novel SLE risk loci, *CAPN13*, *MOB3B/IFNK* and *HAL*, at a suggestive significance threshold ($p<1\times10^{-4}$, online supplemental figure 5B–E, table S8). As the association signals at *CAPN13*, *MOB3B/IFNK* and *HAL* had not been reported in SLE GWAS in other ancestries, we attempted to replicate these findings in additional Scandinavian SLE cases and controls (online supplemental table S1A). However, we did not find additional support for a role of SNVs at these novel loci in SLE (online supplemental table S9).

Patients with SLE carry unique coding variants

We next investigated whether there was an increased rare coding mutational burden for patients with SLE at the 1832 genes. We observed that all individuals carried rare non-synonymous

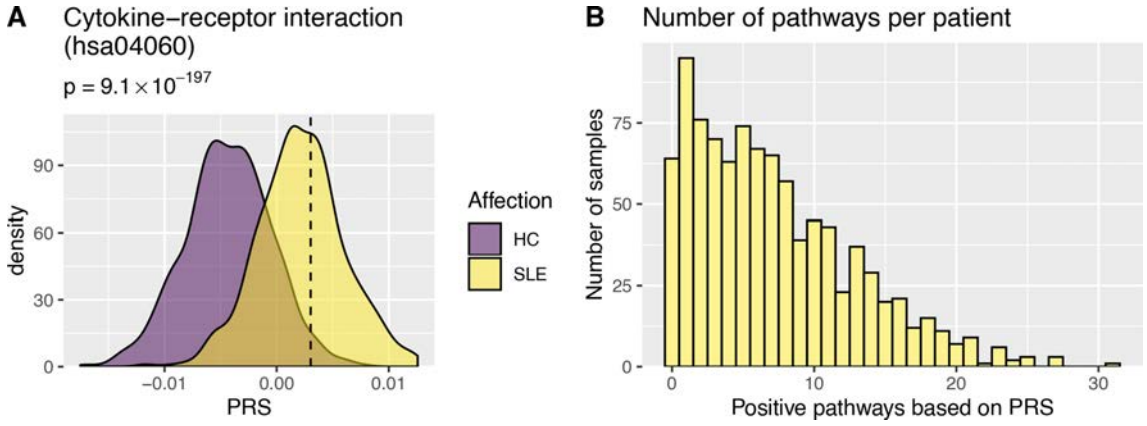

Figure 2 Pathway SLE polygenic risk scores. (A) Illustrates pathway Polygenic Risk Scores (PRS) for the Cytokine–cytokine receptor interaction pathway. P values represent differences in PRS between patients with SLE (SLE) and healthy control individuals (HC). The dashed line indicates the PRS 97.5 percentile in control individuals. (B) The number of pathways each individual patient with SLE tested positive for using the pathway PRS. On average patients were positive for 7.2 pathways. SLE, systemic lupus erythematosus.

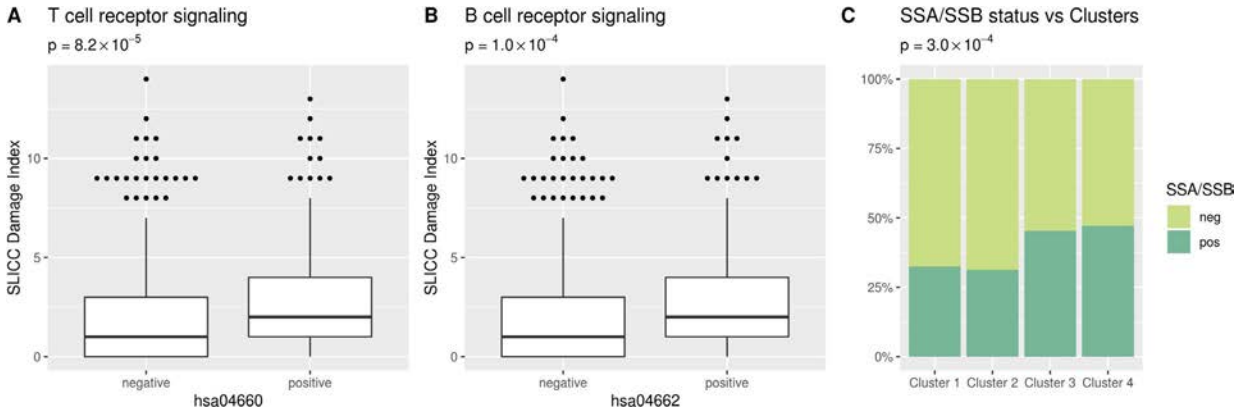

Figure 3 Pathway SLE polygenic risk scores grouping and clustering. (A, B) The Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) damage index for patients with SLE positive and negative for the T cell receptor and B cell receptor signalling pathways. P values represent differences in Damage Index between pathway positive and negative patients, uncorrected p values are presented (Bonferroni corrected threshold p=0.00143). (C) Prevalence of Sjögren's syndrome (SSA and/or SSB) autoantibodies in SLE patients in the four clusters. P value represent difference in SSA/SSB autoantibody status between clusters of SLE patients, uncorrected p value is presented (Bonferroni corrected threshold p=0.002).

variants, with an average number of around 32 variants per individual for both patients with SLE and control individuals (online supplemental figure S6). None of the patients with SLE were homozygous carriers of rare non-synonymous alleles in genes for monogenic SLE and lupus-like diseases (online supplemental table S10). Next, we hypothesised that protein coding variants observed exclusively in patients with SLE could be causal candidates. A total of 1475 case-only nonsynonymous variants were identified in the 958 patients with SLE (online supplemental table S11). These were variants that were observed in at least one patient with SLE, but not in control individuals of similar ancestry.[27 28] The most frequent of these SNVs was found in the *MUC5B* gene which encodes mucin 5B, the major gel-forming mucin in mucus (table 3). Five patients with SLE carried the same deleterious *MUC5B* missense mutation (rs773068050, p.Thr2724Pro). *MUC5B* gene variants have previously been associated with interstitial lung disease (ILD), a condition affecting around 3% of Swedish patients with SLE.[29–31] However, there was no evidence of ILD in these five patients, but two of them had suffered from pleuritis (online supplemental table S12). In conclusion, we did not find evidence for SLE patients carrying a generally increased burden of rare coding variants at these genes. However, our analysis identified a number of coding variants observed exclusively in patients with SLE. This catalogue of variants could serve as a resource for future studies investigating the role of case-only SNVs in SLE.

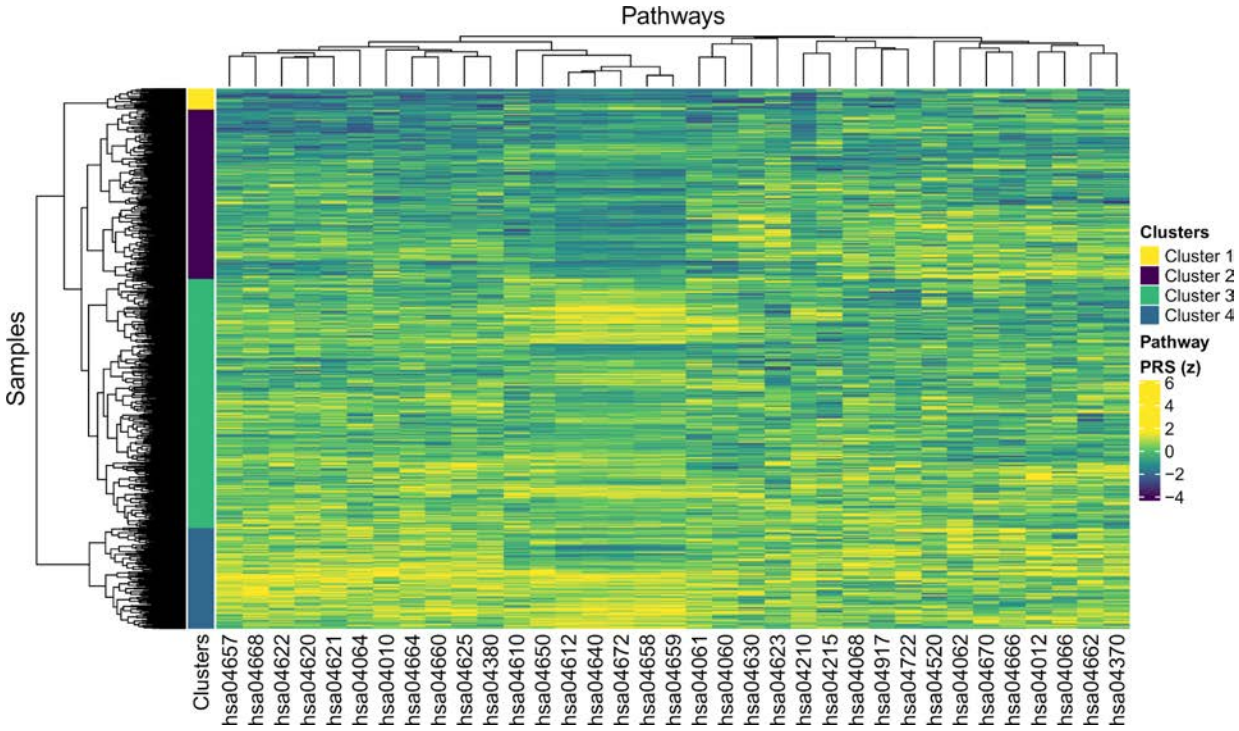

Figure 4 Clustering of patients with SLE based on pathway Polygenic Risk Scores (PRS). Heat map with pathways on the x-axis (KEGG IDs) and individuals on the y-axis based on normalised PRS. Hierarchical cluster analysis was performed based on the PRS per pathway for each individual. The colour bar on the left indicates the four main clusters of individuals identified. KEGG, Kyoto Encyclopaedia of Genes and Genomes; SLE, systemic lupus erythematosus.

Table 2 Gene-set analyses of SLE-associated genes and involved pathways

Set name	Genes tested	No of SNVs all/common/rare	FDR_{ALL}	FDR_{COMMON}	FDR_{RARE}
Interferon (ref 21)	33	4204/849/2866	0.0018	0.66	0.65
Interferonopathy (ref 22,23)	11	2034/463/1271	0.0028	4.1E-07	0.24
SLE GWAS (ref 3,4)	88	18790/5326/11465	1.5E-12	2.0E-15	0.18
Complement*	32	4712/1094/3086	0.00071	2.8E-07	0.20
Monogenic SLE (ref 24)	24	3745/930/2371	2.9E-07	2.9E-11	0.020

All: including all MAFs; Common: MAF >0.05; Rare: MAF <0.01.
*The complement part of KEGG pathway hsa04610.
FDR, false discovery rate; GWAS, genome-wide association study; KEGG, kyoto encyclopedia of genes and genomes; MAF, minor allele frequency; SLE, systemic lupus erythematosus; SNV, single-nucleotide variant.

DISCUSSION

We here suggest a novel pathway-based approach to stratify patients with SLE beyond clinical manifestations. Further, we characterise genetic pathway associations and investigate rare variant contributions to the pathogenesis of SLE, all using targeted sequencing of immunity genes.

Using case–control association testing for immunological pathways, we identified two main axes of SLE association: T cell differentiation and innate immunity pathways. T cells have a fundamental role in loss of tolerance, autoimmunity and inflammatory reactions. In SLE, a number of different T cell disturbances have been described, which can contribute to the generation of autoreactive T cells, aberrant cytokine production and impaired T regulatory cell function.[32] Besides the direct involvement of pathways connected to Th1 and Th2 cells, we noticed association signals from two pathways related to interleukin 17 (IL-17). A proportion of patients with SLE display raised serum levels of IL-17, elevated numbers of circulating IL-17-producing T cells and increased IL-17 production by lymphocytes, suggesting dysregulation of T regulatory cells.[33] Our findings strengthen the recent suggestions that IL-17 inhibition could be a therapeutic option in a subset of patients with SLE.[34] Conversely, low-dose IL-2 treatment in SLE to stimulate T regulatory cells has recently shown promising results.[35]

We observed that the T cell differentiation pathway associations were influenced by genetic associations to HLA, which is not surprising given the essential role of HLA in the immune response. This was further demonstrated by the antigen processing and presentation pathway association dominated by HLA genes. Complement pathway associations are also possibly confounded by the HLA SLE association, since early complement component genes are located in the HLA class III locus on chromosome 6.[36] The JAK-STAT pathway was associated with SLE, it is the main route to initiate gene expression and protein synthesis for over 50 cytokines, many of which are involved in the SLE disease process.[37 38] Variants of a number of genes in the JAK-STAT pathway have been associated with an increased risk for SLE, for instance *STAT4-STAT1* and *TYK2*.[3 4]

Our study highlights the importance of the interferon system in SLE. Previous studies have shown genetic associations at a number of genes in the IFN signalling pathway in SLE.[2 3] Here, we show that, in aggregate, genetic variation at interferonopathy

Table 3 SLE case-only recurrent non-synonymous SNVs

CHR	BP	SNV	Ref allele	Alt allele	Count SLE	Gene	Consequence	Amino acid change	SIFT
11	1 266 280	rs773068050	A	C	5	*MUC5B*	Missense variant	p.Thr2727Pro	Deleterious(0.05)
1	186 363 103	rs1292231132	C	A	4	*C1orf27*	Missense variant	p.Gln246Lys	Tolerated(0.21)
1	151 342 270	rs772030489	G	T	2	*SELENBP1*	Missense variant	p.Pro36Thr	Deleterious low confidence(0.01)
2	27 455 971	rs776014297	T	A	2	*CAD*	Missense variant	p.Met922Lys	Deleterious(0.04)
2	179 698 928	rs892049188	G	A	2	*CCDC141*	Missense variant	p.Ser1522Phe	Tolerated(0.08)
9	16 431 447	chr9:16 431 447	G	A	2	*BNC2*	Missense variant	p.His307Tyr	–
9	21 166 175	rs779242420	T	C	2	*IFNA21*	Missense variant	p.Tyr146Cys	Deleterious(0.01)
10	75 583 821	chr10:75 583 821	G	T	2	*CAMK2G*	Missense variant	p.His370Asn	Deleterious low confidence(0.03)
12	6 458 353	rs775543049	G	A	2	*SCNN1A*	Stop gained	p.Arg551*	–
12	48 482 728	rs750735162	T	C	2	*SENP1*	Missense variant	p.Thr155Ala	Deleterious low confidence(0)
12	56 350 882	rs1425141530	G	T	2	*PMEL*	Missense variant	p.Pro402His	Deleterious(0.02)
12	129 190 793	rs1386045604	C	G	2	*TMEM132C*	Missense variant	p.Pro1094Ala	Tolerated(0.21)
14	23 057 866	chr14:23 057 866	A	T	2	*DAD1*	Missense variant	p.Ser66Arg	Deleterious(0.04)
15	91 030 272	rs181919733	G	A	2	*IQGAP1*	Missense variant	p.Val1371Met	Tolerated(0.07)
17	41 143 320	rs1456586259	G	A	2	*RUNDC1*	Missense variant	p.Val477Ile	Tolerated(0.12)
19	4 891 395	rs139019426	T	C	2	*ARRDC5*	Missense variant	p.Gln231Arg	Tolerated(0.86)
19	18 273 781	rs777121279	G	A	2	*PIK3R2*	Missense variant	p.Gly372Ser	Deleterious(0)
19	55 240 959	rs764066889	G	A	2	*KIR3DL3*	Missense variant, splice region variant	p.Gly219Asp	Deleterious(0.02)

SIFT (Sorting Intolerant From Tolerant) prediction whether the amino acid substitution affects protein function.
BP, base pair; CHR, chromosome; SLE, systemic lupus erythematosus; SNV, single-nucleotide variant.

genes also contribute to risk for SLE. In addition to interferonopathy genes, we also observed an aggregate genetic association for monogenic SLE and lupus-like disease genes with both a rare and a common variant contribution. This supports the hypothesis of a shared genetic basis and consequently disease mechanisms between monogenic and complex forms of disease, where also common non-coding variants can affect the regulation of Mendelian disease genes resulting in clinically similar traits.[39]

We have previously demonstrated that an SLE genetic risk score was associated with disease severity in SLE.[5] We here generated a pathway-centred SLE PRS and found that there was a large variation in the number of affected pathways among the patients, which underscores the heterogeneity of SLE. We observed higher SLE damage indexes in patients with SLE positive for the B or T cell receptor signalling pathways, thus, pathways in the adaptive immune system seem important for the long-term severity of the disease. This is in accordance with previous findings that SLE disease activity correlates with abnormal B lymphocyte activity and T cell abnormalities, as well as the connection between disease activity and accumulation of organ damage.[40 41]

We attempted to cluster patients into subsets with shared genetic pathway profiles, which suggested four subgroups of patients with SLE. Beside the SSA/SSB antibody profile, these clusters were not connected to clinical disease manifestations such as nephritis or survival. This observation may indicate that the PRS reflects part of the central autoimmune process, which is not translated into specific organ manifestations. Whether the PRS in individual patients with SLE, or the different clusters, contribute to treatment response is an interesting possibility, but could not be assessed in this study. This is one limitation of our study, together with the fact that our conclusions apply specifically to this set of candidate genes.

WGS or WES studies will be required to fully elucidate the role of rare variants and pathways in SLE. As previously shown by us and others, WGS and WES in selected patients can provide information on ultrarare and de novo SNVs in SLE.[6 7 42] However, larger sample sizes than those reported to date will be required to paint a complete picture of the genetic aetiology of SLE. We did not find support in additional Scandinavian cohorts for a role in SLE for the novel loci identified in the Swedish cohorts. Possible explanations include overestimated effect sizes in the discovery cohort, differences in genetic background within Scandinavia, or differences in clinical manifestations or characterisation of patients. Lastly, our study identified a large number of case-only coding variants. Variants uniquely identified in patients could be causal candidates in SLE, but their statistical significance is difficult to evaluate.

In summary, we have suggested a novel strategy to genetically stratify patients with SLE according to involved molecular pathways. T cell pathways displayed the strongest association, which highlights the importance of the adaptive immune system in the disease. The strong connection to the JAK-STAT pathway, including the IFN system, is perhaps not surprising given the promising clinical trials of JAK and type I interferon receptor inhibition as treatments for SLE.[38 43 44] However, not all patients in these studies respond to treatment, and dissecting affected molecular pathways in responders and non-responders could increase the understanding of treatment outcome. This approach has not been tested clinically, but the future of precision medicine for SLE lies in identifying robust methods to perform molecular stratification of patients.

Author affiliations
[1]Department of Medical Sciences, Rheumatology, Uppsala University, Uppsala, Sweden
[2]Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden
[3]Department of Psychiatry, Washington University, St. Louis, Missouri, USA
[4]Division of Rheumatology, Department of Medicine, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden
[5]Department of Public Health and Clinical Medicine/Rheumatology, Umeå University, Umeå, Sweden
[6]Broegelmann Research Laboratory, Department of Clinical Science, University of Bergen, Bergen, Norway
[7]Clinical Immunology unit, Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway
[8]Department of Medical Genetics, University of Oslo, Oslo, Norway
[9]Institute for Inflammation Research, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[10]Department of Clinical Immunology, Aalborg University, Aalborg, Denmark
[11]Department of Clinical Immunology, Odense University Hospital, Odense, Denmark
[12]Department of Rheumatology, Oslo University Hospital, Oslo, Norway
[13]Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[14]Department of Rheumatology, Odense University Hospital, Odense, Denmark
[15]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark
[16]Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark
[17]Center for Rheumatology and Spine Diseases, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[18]Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[19]Department of Medical Sciences, Molecular Medicine and Science for Life Laboratory, Uppsala University, Uppsala, Sweden
[20]Department of Clinical Sciences Lund, Rheumatology, Lund University, Skane University Hospital, Lund, Sweden
[21]Department of Biomedical and Clinical Sciences, Division of Inflammation and Infection, Linköping University, Linköping, Sweden
[22]Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA

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Collaborators The DISSECT consortium: Johanna K. Sandling (Department of Medical Sciences, Rheumatology, Uppsala University, Uppsala, Sweden), Pascal Pucholt (Department of Medical Sciences, Rheumatology, Uppsala University, Sweden), Lina Hultin Rosenberg (Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden), Fabiana H.G. Farias (Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden, and Department of Psychiatry, Washington University, St. Louis, MO, USA), Sergey V. Kozyrev (Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden), Maija-Leena Eloranta (Department of Medical Sciences, Rheumatology, Uppsala University, Uppsala, Sweden), Andrei Alexsson (Department of Medical Sciences, Rheumatology, Uppsala University, Uppsala, Sweden), Matteo Bianchi (Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden), Leonid Padyukov (Division of Rheumatology, Department of Medicine, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden), Christine Bengtsson (Department of Public Health and Clinical Medicine/Rheumatology, Umeå University, Umeå, Sweden), Roland Jonsson (Broegelmann Research Laboratory, Department of Clinical Science, University of Bergen, Bergen, Norway), Roald Omdal (Clinical Immunology unit, Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway and Broegelmann Research Laboratory, Department of Clinical Science, University of Bergen, Bergen, Norway), Øyvind Molberg (Department of Rheumatology, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway), Ann-Christine Syvänen (Department of Medical Sciences, Molecular Medicine and Science for Life Laboratory, Uppsala University, Uppsala, Sweden), Andreas Jönsen (Lund University, Skane University Hospital, Department of Clinical Sciences Lund, Rheumatology, Lund, Sweden), Iva Gunnarsson (Division of Rheumatology, Department of Medicine Solna, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden), Elisabet Svenungsson (Division of Rheumatology, Department of Medicine Solna, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden), Solbritt Rantapää-Dahlqvist (Department of Public Health and Clinical Medicine/Rheumatology, Umeå University, Umeå, Sweden), Anders A. Bengtsson (Lund University, Skane University Hospital,

Department of Clinical Sciences Lund, Rheumatology, Lund, Sweden), Christopher Sjöwall (Department of Biomedical and Clinical Sciences, Division of Inflammation and Infection, Linköping University, Linköping, Sweden), Dag Leonard (Department of Medical Sciences, Rheumatology, Uppsala University, Uppsala, Sweden), Kerstin Lindblad-Toh (Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden and Broad Institute of MIT and Harvard, Cambridge, MA, USA), Lars Rönnblom (Department of Medical Sciences, Rheumatology, Uppsala University, Uppsala, Sweden), Jonas Carlsson Almlöf (Department of Medical Sciences, Molecular Medicine and Science for Life Laboratory, Uppsala University, Uppsala, Sweden), Johanna Dahlqvist (Science for Life Laboratory, Department of Medical Sciences and Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden), Daniel Eriksson (Department of Medicine (Solna), Karolinska Institutet, and Department of Endocrinology, Metabolism and Diabetes Karolinska University Hospital, Stockholm, Sweden), Niklas Hagberg (Department of Medical Sciences, Rheumatology, Uppsala University, Uppsala, Sweden), Ingrid E. Lundberg (Division of Rheumatology, Department of Medicine and Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden), Argyri Mathioudaki (Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden), Jennifer Meadows (Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden), Jessika Nordin (Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden), Gunnel Nordmark (Department of Medical Sciences, Rheumatology, Uppsala University, Uppsala, Sweden), Marie Wahren-Herlenius (Department of Medicine, Division of Rheumatology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden and Broegelmann Research Laboratory, Department of Clinical Science, University of Bergen, Norway), Sule Yavuz (Department of Medical Sciences, Rheumatology, Uppsala University, Uppsala, Sweden). The ImmunoArray development consortium: Kerstin Lindblad-Toh (Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden and Broad Institute of MIT and Harvard, Cambridge, MA, USA), Gerli Rosengren Pielberg (Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden), Anna Lobell (Office for Medicine and Pharmacy, Uppsala University, Uppsala, Sweden), Åsa Karlsson (Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden), Eva Murén (Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden), Göran Andersson (Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences, Uppsala, Sweden), Kerstin M. Ahlgren (Department of Surgical Sciences, Uppsala University, Uppsala, Sweden), Lars Rönnblom (Department of Medical Sciences, Rheumatology, Uppsala University, Uppsala, Sweden), Maija-Leena Eloranta (Department of Medical Sciences, Rheumatology, Uppsala University, Uppsala, Sweden), Nils Landegren (Department of Medicine (Solna), Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden and Science for Life Laboratory, Department of Medical Sciences, Uppsala University, Uppsala, Sweden), Olle Kämpe (Department of Medicine (Solna), Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden, Department of Endocrinology, Metabolism and Diabetes Karolinska University Hospital, Stockholm, Sweden, Science for Life Laboratory, Department of Medical Sciences, Uppsala University, Uppsala, Sweden and KG Jebsen Center for autoimmune diseases, University of Bergen, Norway), Peter Söderkvist (Division of Cell Biology, Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden).

Contributors KLT and LR conceived and designed the experiments. CB, KL, AV, AMT, SJ, AJ, IG, ES, SR-D, AAB, CS and DL characterised the patient samples. M-LE, LP, LM, RS, MAJ, RJ, RO, BAL and STL provided samples and data. The ImmunoArray development consortium members designed the targeted sequencing panel. FHGF, SVK, ÅK, and EM performed the experiments. A-CS managed the sequencing platform. JKS, LHR, PP, AA and MB analysed the data and the DISSECT consortium members provided intellectual input and/or developed analysis pipelines. JKS and LR wrote the manuscript. All authors read, provided critical review and accepted the final version of the manuscript.

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ORCID iDs
Johanna K Sandling http://orcid.org/0000-0003-1382-2321
Pascal Pucholt http://orcid.org/0000-0003-3342-1373
Elisabet Svenungsson http://orcid.org/0000-0003-3396-3244
Christopher Sjöwall http://orcid.org/0000-0003-0900-2048
Lars Rönnblom http://orcid.org/0000-0001-9403-6503

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TRANSLATIONAL SCIENCE

Genomic Risk Score impact on susceptibility to systemic sclerosis

Lara Bossini-Castillo,[1] Gonzalo Villanueva-Martin ,[2] Martin Kerick,[2] Marialbert Acosta-Herrera,[2] Elena López-Isac,[2] Carmen P Simeón,[3] Norberto Ortego-Centeno,[4] Shervin Assassi ,[5] International SSc Group, Australian Scleroderma Interest Group (ASIG), PRECISESADS Clinical Consortium, PRECISESADS Flow Cytometry study group, Nicolas Hunzelmann,[6] Armando Gabrielli,[7] J K de Vries-Bouwstra,[8] Yannick Allanore ,[9] Carmen Fonseca,[10] Christopher P Denton ,[10] Timothy RDJ Radstake,[11] Marta Eugenia Alarcón-Riquelme,[12] Lorenzo Beretta ,[13] Maureen D Mayes,[5] Javier Martin[2]

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For numbered affiliations see end of article.

Correspondence to
Dr Lara Bossini-Castillo, Departamento de Genética e Instituto de Biotecnología, Universidad de Granada, Centro de Investigación Biomédica (CIBM), Parque Tecnológico Ciencias de la Salud, Avenida del Conocimiento, s/n, 18016, Armilla (Granada), Andalucía, Spain; lbossinicastillo@ugr.es and Dr Javier Martin, Institute of Parasitology and Biomedicine López-Neyra, IPBLN. Consejo Superior de Investigaciones Científicas (CSIC). Parque Tecnológico de Ciencias de la Salud. Avenida del Conocimiento, 17, 18016, Armilla (Granada), Andalucía, Spain; javiermartin@ipb.csic.es

LB-C and GV-M contributed equally.

LB-C and GV-M are joint first authors.

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ABSTRACT

Objectives Genomic Risk Scores (GRS) successfully demonstrated the ability of genetics to identify those individuals at high risk for complex traits including immune-mediated inflammatory diseases (IMIDs). We aimed to test the performance of GRS in the prediction of risk for systemic sclerosis (SSc) for the first time.

Methods Allelic effects were obtained from the largest SSc Genome-Wide Association Study (GWAS) to date (9 095 SSc and 17 584 healthy controls with European ancestry). The best-fitting GRS was identified under the additive model in an independent cohort that comprised 400 patients with SSc and 571 controls. Additionally, GRS for clinical subtypes (limited cutaneous SSc and diffuse cutaneous SSc) and serological subtypes (anti-topoisomerase positive (ATA+) and anti-centromere positive (ACA+)) were generated. We combined the estimated GRS with demographic and immunological parameters in a multivariate generalised linear model.

Results The best-fitting SSc GRS included 33 single nucleotide polymorphisms (SNPs) and discriminated between patients with SSc and controls (area under the receiver operating characteristic (ROC) curve (AUC)=0.673). Moreover, the GRS differentiated between SSc and other IMIDs, such as rheumatoid arthritis and Sjögren's syndrome. Finally, the combination of GRS with age and immune cell counts significantly increased the performance of the model (AUC=0.787). While the SSc GRS was not able to discriminate between ATA+ and ACA+ patients (AUC<0.5), the serological subtype GRS, which was based on the allelic effects observed for the comparison between ACA+ and ATA+ patients, reached an AUC=0.693.

Conclusions GRS was successfully implemented in SSc. The model discriminated between patients with SSc and controls or other IMIDs, confirming the potential of GRS to support early and differential diagnosis for SSc.

Key messages

What is already known about this subject?
- Systemic sclerosis (SSc) is a complex immune-mediated disease (IMID) for which a Genomic Risk Score (GRS) has never been implemented.

What does this study add?
- A SSc GRS discriminates between patients with SSc and healthy controls with a remarkable predictive value.
- Clinical information, such as serologic subtype and immune cells counts, adds accuracy to the GRS model.
- The SSc GRS is capable of discriminating between SSc and other IMIDs.

How might this impact clinical practice or future developments?
- This SSc GRS is a promising tool to improve the diagnosis and prognosis of patients with SSc.

INTRODUCTION

Complex diseases are a devastating consequence of usually unknown environmental factors and the combined effects of tens to thousands of genetic variants that are spread throughout the genome.[1] The advanced use of bioinformatic tools will provide a better understanding of the intricate network of multiple genetic effects that shapes the architecture of complex diseases.[2]

Immune-mediated inflammatory diseases (IMIDs) comprise a variety of complex diseases characterised by the loss of self-tolerance, the maintenance of chronic inflammation and an aberrant immune response.[3] Genome-wide association studies (GWAS) have largely increased our understanding of the aetiology of complex diseases, providing new data about the genome and lighting the way to the identification of genes and pathways that contribute to disease susceptibility and prognosis. Many susceptibility loci have been discovered for IMIDs, and several are shared between diseases, adding a common genetic background to their overlapping clinical and immunological characteristics.[4] Additionally, GWAS findings have also confirmed that the contribution of

each associated locus to disease risk is often small and has low predictive value.[1]

To address complex disease susceptibility, three main components must be considered: genetics, environmental exposures and lifestyle factors.[1 4] As for genetics, large cohorts have been genotyped in GWAS efforts, and hundreds of genetic risk factors have been identified.[5] However, GWAS data can be examined in various ways, moving forward to a more precise genetic profiling, its use for personalised medicine and the identification of individuals with higher risk of displaying a specific phenotype.[6] Genomic Risk Scores (GRS) take into account disease heritability and the additive effect of genetic polymorphisms, and they provide a disease risk score per individual to evaluate their relative risk to suffer a disease.[7–9]

GRS are calculated essentially by combining the weighted effects of the risk alleles for each individual; these weighted effects are assigned depending on the strength of the association to the risk of disease—the effect size.[7 10] The identification of individuals with high risk or those prone to developing more aggressive phenotypes is a useful tool for personalised medicine and clinical management of patients. GRS have been successful in several diseases such as schizophrenia[11] and obesity.[12] This strategy had a great impact on cardiovascular diseases such as coronary artery disease[12–14] but also in IMIDs such as sarcoidosis,[15] systemic lupus erythematosus (SLE)[16 17] and vitiligo[18] recently.

Systemic sclerosis (SSc) or scleroderma is a complex chronic autoimmune disease. It belongs to the group of IMIDs and it has one of the highest mortality rates among them.[19] SSc affects the connective tissue and shows complex and varied clinical manifestations. Raynaud's phenomenon and gastro-oesophageal reflux are two common onset symptoms, but they are not exclusive to SSc. Conversely, the disease can manifest in different ways, such as affectation of the skin (inflammatory skin disease, extensive fibrosis), musculoskeletal inflammation and vascular damage.[20–22] Furthermore, SSc also shows organ-specific manifestations, such as lung fibrosis, pulmonary arterial hypertension, renal failure and gastrointestinal complications. Notably, the involvement of the lungs, with pulmonary hypertension and/or pulmonary fibrosis, is the leading cause of death in SSc.[19]

Patients with SSc can be classified into different subgroups according to clinical outcome: limited cutaneous scleroderma (lcSSc) or diffuse cutaneous scleroderma (dcSSc), depending on how widespread fibrosis is.[23] On other hand, they can also be classified depending on their serological status, considering the presence of the mutually exclusive anti-centromere or anti-topoisomerase autoantibodies (ie, ACA+ or ATA+).[22 23]

Since the first SSc GWAS in European populations was carried out 10 years ago,[24] our recently published meta-GWAS is the largest effort to decipher the genetic component of SSc.[25] In addition to the extensively known association of the human leucocyte antigen (HLA) region with the disease, 27 non-HLA GWAS level associations and 3 suggestive loci were identified.[25]

Considering the heterogeneity and variable prognosis of patients with SSc, GRS could be a powerful tool in clinical diagnosis to identify patients in the early stages of the disease and to differentiate them from patients with confounding diseases. By taking advantage of the summary statistics of this large meta-GWAS, we generated an accurate SSc GRS through the use of an independent and unique dataset comprising patients with SSc and with other IMIDs[3] (figure 1). We generated subtype-specific GRS for the clinical and serological SSc subgroups of patients, and we tested the clinical implications of GRS in SSc. Finally, the GRS was complemented with additional demographic and immunological information.

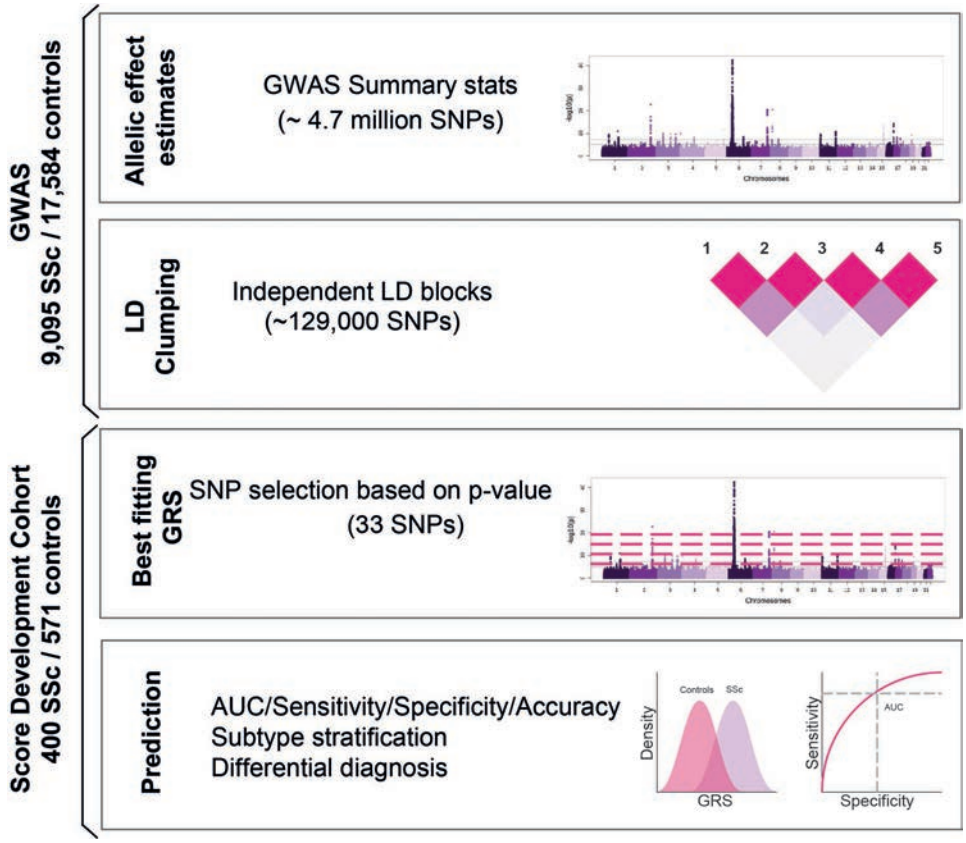

Figure 1 Overview of the study design. AUC, area under the receiver operating characteristic (ROC) curve; GRS, Genomic Risk Scores; GWAS, genome-wide association studies;SNPs, single nucleotide polymorphisms.

METHODS

GRS calculation

GRS was developed as implemented in PRSice-2,[26] using summary statistics and assuming an additive effect for the effective allele. Briefly, PRSice-2 calculated the product of the number of effect alleles per individual and the respective SNP weights. The score was averaged by the number of alleles included in the GRS per individual (argument --score avg). We used the minor allele frequency in the PRECISESADS cohort as the genotype for the samples with missing genotype. We applied a 10 000 permutation procedure to calculate the empirical p value (--perm 10 000).

PRSice-2 allowed us to fit different GRS models by selecting only the variants that passed a number of different p value thresholds in the GWAS summary statistics (argument --bar-levels 5e-11, 5e-10, 5e-09, 5e-08, 5e-07, 5e-06, 5e-05, 0.0001, 0.001, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 1, but GRS calculated at all intermediate p value thresholds, high resolution parameters, were calculated) using sex (female/male) as covariate. Therefore, the model fit is defined as: R^2 of the full model (SSc case or control ~ GRS + Sex) − R^2 of the null model (SSc case or control ~ Sex).

Multivariate model

In order to test if a combination of GRS with demographic factors and the counts of immune cell subpopulations in peripheral blood would improve the predictive value of our model, we divided our score development cohort into an initial set, comprising the non-Spanish individuals in the PRECISESADS study (n=518), in which we developed a multivariate model and a testing set that comprised all the Spanish individuals in this study (n=339).

First, we built several generalised linear models that included GRS and each demographic and immune parameter in online supplemental table 1 individually, then we compared them to the null model that included only GRS and sex as covariates. Improvement over the null model was defined by an LRT (p value<0.05).

Second, we generated a multivariate model that included the 13 phenotypic variables that had been identified as informative in the previous step. Using leave-one-out prediction (ie, including all variables but one in the model) and comparing to the full model, we calculated the contribution of all variables to the multivariate model. This model was applied to the testing set of individuals.

Details about the cohorts, linkage disequilibrium (LD) clumping, GRS additive model, the model fitting analyses and the effects of including country of origin as covariates are shown in the online supplemental methods section.

RESULTS

A 33-variant GRS discriminates between patients with SSc and controls

We calculated GRS in an independent score development cohort comprising 400 patients with SSc and 571 healthy controls.[27] We observed that the best-fitting GRS (GRS R^2=0.13; p value=1.27×10^{-17}; permutation p value=9.99×10^{-5}) included 33 independent SNPs that had a p value<2.215×10^{-7} (figure 2A). Sex, which was included as a covariate, contributed very modestly to the explained variance (R^2=0.01).

As expected, the SSc cases and controls showed significantly different GRS distributions (figure 2B, control group mean=-8.35×10^{-3} and SSc group mean=-1.91×10^{-3}, t-test p value<2.2×10^{-16}). Reassuringly, individuals with GRS in the 95th percentile showed a fivefold higher relative risk (OR=7.89, 95% CI 3.44 to 18.08) than the reference quantile (40th–60th percentiles) (figure 2C).

Reassuringly, the 33 variant GRS had a 67% chance of accurately predicting if an individual was a patient with SSc or an unaffected control (AUC=0.673, 95% CI 0.64 to 0.71, p value=3.90×10^{-23}, figure 2D). We determined a best-fitting GRS threshold (GRS controls<-1.86×10^{-3}<GRS cases, details in online supplemental methods) and reached a moderate discrimination between cases and controls (specificity=0.76; sensitivity=0.51; accuracy=0.66, figure 2D).

We observed that if the receiver operating characteristic (ROC) curves were calculated separately for each country of origin, the AUC determined by the 33 variant GRS ranged from 0.60 to 0.75 (online supplemental figure 2A). However, variability of the AUC did not correlate with either country longitude, latitude or distance to 1000 genomes GBR and CEU populations (see online supplemental methods, online supplemental figure 2B-D).

Subtype stratified SSc GWAS summary stats discriminate between clinical and serological subtypes

The 33 variant GRS previously described distinguished between patients with SSc and healthy controls. However, SSc is a heterogeneous disease with both clinical and serological subtypes that influence the prognosis of the disease, and the prediction of these subtypes is a major clinical demand. The 33 SNP SSc GRS showed no predictive value for clinical subtypes (dcSSc vs lcSSc AUC=0.496, 95% CI 0.40 to 0.59, p value=0.93, online supplemental figure 3) and serological subtypes (ATA+ vs ACA+ AUC = 0.464, 95% CI 0.37 to 0.56, p value=0.45, online supplemental figure 3). Furthermore, this SSc GRS was not able to predict the development of pulmonary fibrosis in patients with SSc (SSc with pulmonary fibrosis vs SSc without pulmonary fibrosis AUC=0.479, 95% CI 0.38 to 0.57, p value=0.66, online supplemental figure 3).

Therefore, we used the allelic effects obtained in the GWAS comparison between dcSSc and lcSSc and between ATA+ and ACA+ patients to build subtype-specific GRS. The best-fitting GRS p value threshold for the variants in the dcSSc versus lcSSc comparison, clinical subtype GRS, comprised up to 9780 SNPs (SNP p value threshold for the best- fitting dcSSc vs lcSSc GRS <9.99×10-2, figure 3A). This clinical subtype GRS was not limited to highly significant variants but it also included thousands of additional SNPs with very low significance. The GRS for the variants in the ATA+ vs ACA+ comparison, serological subtype GRS, required up to 35 058 SNPs (SNP p value threshold for the best-fitting ATA+ vs ACA+ GRS < 3.48×10^{-1}, figure 3A). The clinical subtype GRS did not explain much of the phenotypic variance between dcSSc and lcSSc (R^2=0.053), while the explained variance between them using the serological subtype GRS was comparable with the SSc GRS (R^2=0.115). In this context, the subtype-specific GRS distributions (mean dcSSc GRS=2.46×10^{-3}; mean lcSSc GRS=2.16×10^{-3}; t-test p value=1.21×10^{-2}, figure 3B), and AUC based on the clinical subtype GRS led to a modest classification of the patients into the dcSSc or lcSSc groups (AUC=0.604, 95% CI 0.51 to 0.70, p value=2.59×10^{-2}, figure 3C). However, the serological subtype GRS (comprising 35 058 SNPs) showed more distinctive GRS distributions between ATA+ and ACA+ patients (mean ATA+ GRS = 1.39×10^{-3} and mean ACA+ GRS=1.11×10^{-3}, t-test p value=1.12×10^{-4}, figure 3B), and best classification results for the ATA+ or ACA+ subgroups of patients (AUC=0.693, 95% CI 0.61 to 0.78, p value=7.58×10^{-6}, figure 3C).

Considering the clinical relevance of pulmonary fibrosis for the prognosis of patients with SSc, we tested the predictive value of both the clinical and the serological GRS on the development of lung fibrosis. Interestingly, we observed that the serological GRS was marginally able to discriminate between patients with

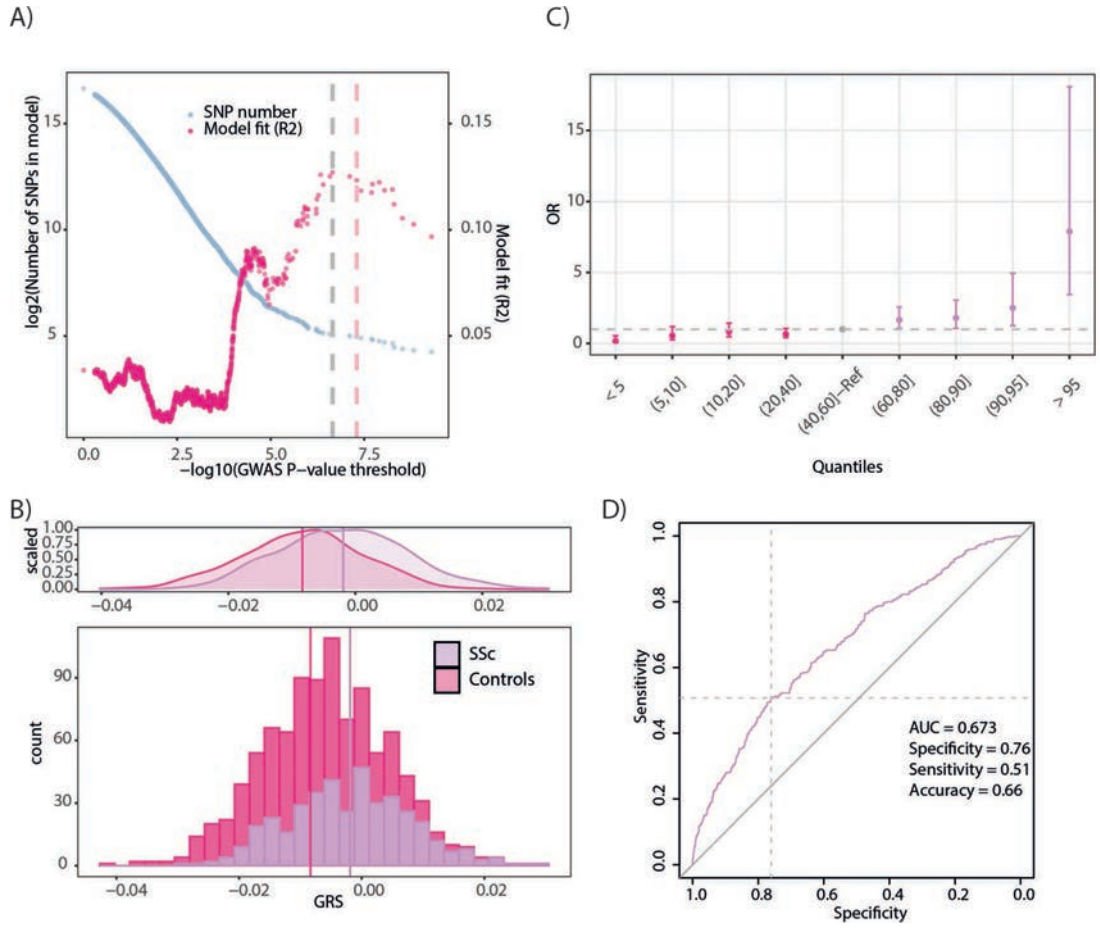

Figure 2 Systemic sclerosis Genomic Risk Scores (SSc GRS). (A) Identification of the best-fitting GRS in the score development cohort. Tested p value thresholds for the SNPs included in the GWAS summary statistics are presented in the x-axis. The number of SNPs included in the models corresponding to each p value threshold is shown on the left y-axis. Model fit (R^2) is represented in the right y-axis. (B) Distribution of GRS for patients with SSc and healthy controls in the score development cohort. (C) Relative risk for individuals in different quantiles of the GRS distribution. (D) receiver operating characteristic (ROC) curve for the 33 SNP SSc GRS. AUC, area under the ROC curve; GWAS, genome-wideassociation studies; SNPs, single nucleotide polymorphisms.

and without lung fibrosis but the model did not reach statistical significance (AUC=0.575, 95% CI 0.48 to 0.67, p value=0.11, online supplemental figure 3).

GRS separates SSc from other IMIDs

Considering the shared genetic component of IMIDs, the implementation of the proposed GRS might help to identify high-risk individuals not only for SSc but also for other immune-related traits. Regarding the accuracy of the 33 variant SSc GRS in other IMIDs, we observed that the SSc GRS was able to separate patients with RA (RA group mean=-4.46×10^{-3}; t-test p value<2.8×10^{-9}), Sjögren syndrome, SJS (SJS group mean=-1.78×10^{-3}; t-test p value<3.54×10^{-6}) and SLE (SLE group mean=-3.67×10^{-3}; t-test p value<8.51×10^{-13}) from the non-affected individuals. However, as expected, the GRS differences between patients with RA, SJS and SLE and controls were less significant than between SSc cases and controls (figure 4A). Furthermore, using the SSc GRS in these three additional IMIDs, the AUCs showed a modest predictive value (AUC RA=0.608, 95% CI 0.57 to 0.64, p value=6.58×10^{-9}; SJS=0.590, 95% CI 0.55 to 0.63, p value=1.58×10^{-6}; AUC SLE=0.623, 95% CI 0.59 to 0.66, p value=3.94×10^{-12}, figure 4B).

A key point toward GRS being implemented from bench-to-bedside is not only the ability to identify individuals at high risk of developing SSc in the general population, but also to help in the differential diagnosis between SSc and other IMIDs. In the pursuit of this objective, we tested the effectiveness of our SSc GRS to correctly classify between patients with SSc and those affected by other IMIDs. We report statistical differences between the GRS distributions for SSc and rheumatoid arthritis (RA) (t-test p value<3.78×10^{-4}) or SJS (t-test p value<3.70×10^{-6}), but only nominally significant differences in the case of SLE (t-test p value<1.37×10^{-2}) (figure 4A). These results were aligned with the predictive capacity of the GRS in the separation between patients with SSc and other IMIDs. The greatest AUC was observed for the classification of patients with SSc versus patients with SJS (SJS AUC=0.585, 95% CI 0.55 to 0.62, p value=2.22×10^{-5}), and decreased in more closely related IMIDs, such as RA (AUC RA=0.568, 95% CI 0.53 to 0.61, p value=8.84×10^{-4}) and, especially, SLE (SLE AUC=0.553, 95% CI 0.51 to 0.59, p value=1.19×10^{-2}) (figure 4C).

Age and immune cell counts improve the prediction accuracy

The score development cohort recruited in the PRECISESADS study was comprehensively phenotyped and allowed us to complement our GRS with additional demographic (age, sex) and immunological (immune cell counts in peripheral blood estimated using a large flow cytometry panel) parameters[28] (online supplemental table 1). We divided our score development cohort into an initial set (n=518) and a testing subgroup (n=339). The

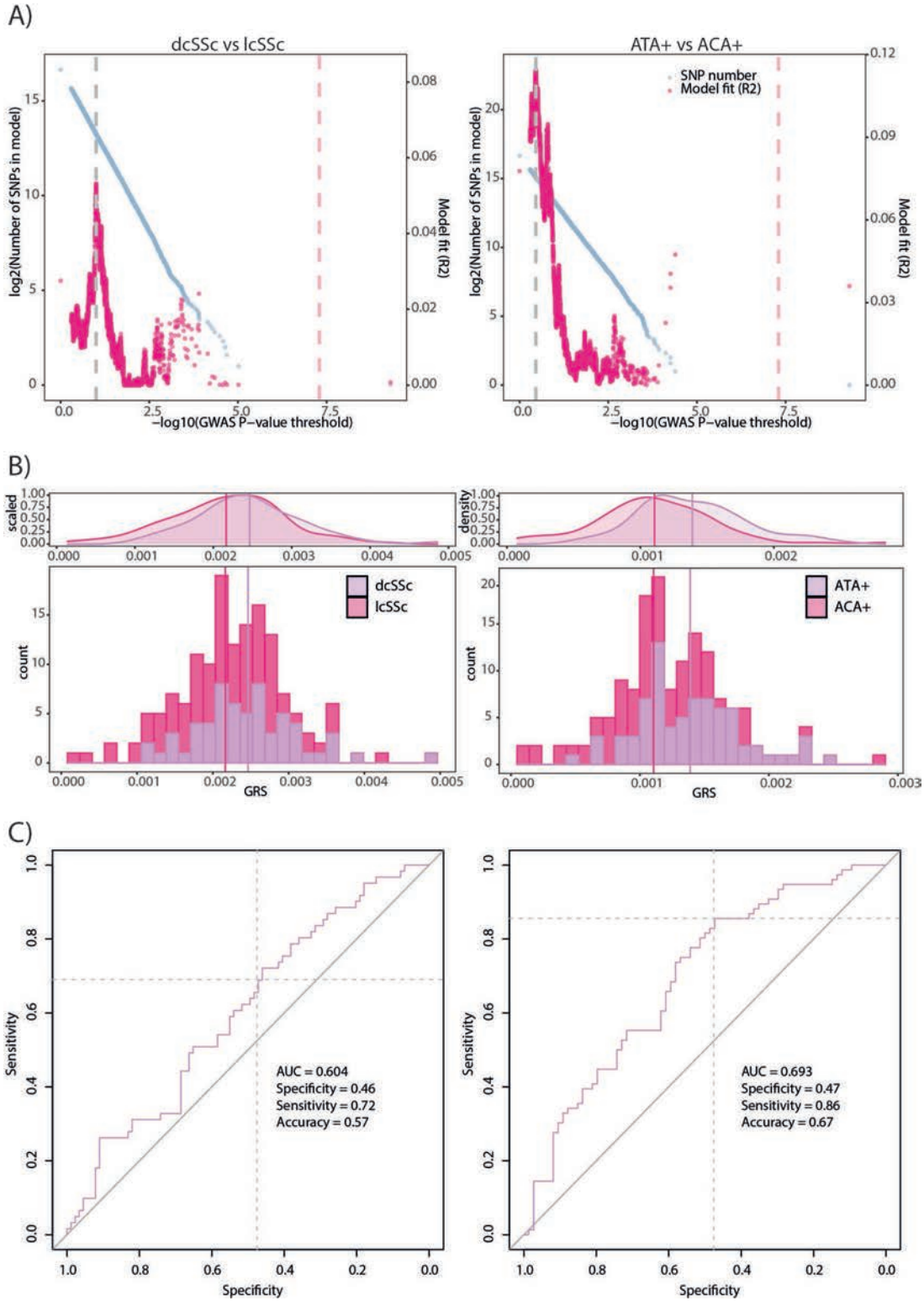

Figure 3 Characteristics of clinical subtype-specific Genomic Risk Scores (GRS) (left) and serological subtype-specific GRS (right). (A) Identification of the best-fitting GRS in the score development cohort. Tested p value thresholds for the SNPs included in the GWAS summary statistics are presented in the x-axis. The number of SNPs included in the models corresponding to each p value threshold is shown on the left y-axis. Model fit (R^2) is represented in the right y-axis. (B) Distribution of GRS for patients with systemic sclerosis (SSc) in each subtype group. (C) Receiver operating characteristic (ROC) curves for the 9 780 SNP clinical subtype-specific GRS and 35 058 SNP serological subtype-specific GRS. AUC, area under the ROC curve; SNPs, single nucleotide polymorphisms.

initial set allowed us to test the relevance of the different parameters in a combined GRS and phenotypic model. On the other hand, the testing set confirmed these findings.

First, we identified the demographic and immunological parameters which improved the GRS model (LRT p value<0.05) (online supplemental table 1). Twelve immune cell subtypes in

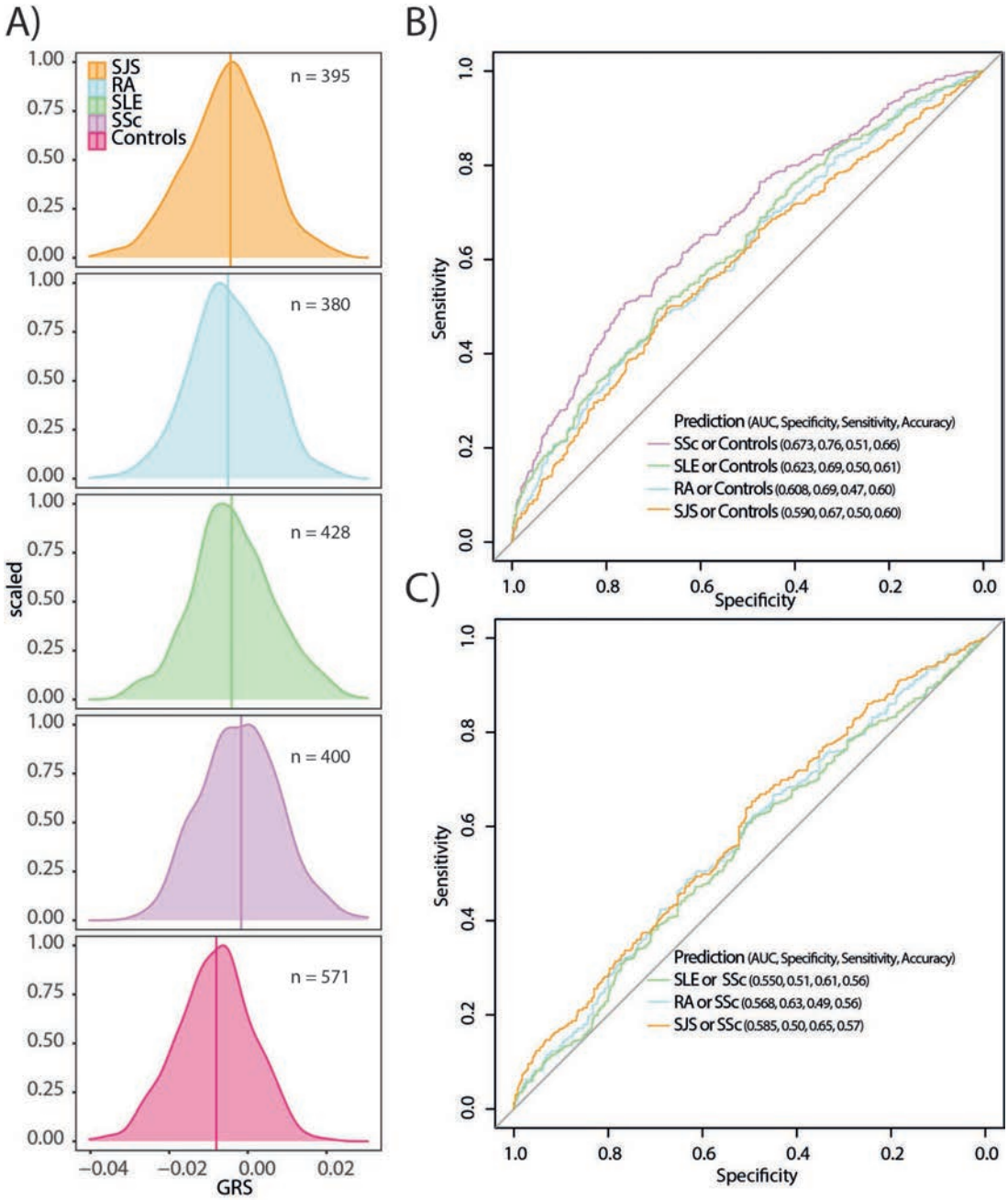

Figure 4 Impact of the 33 SNP systemic sclerosis (SSc) Genomic Risk Scores (GRS) on the differential classification with other immune-mediated inflammatory diseases IMIDs). (A) Distribution of GRS for healthy controls and patients with SSc, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and Sjögren syndrome (SJS). (B) Receiver operating characteristic (ROC) curves for the predictive value of the SSc GRS to distinguish between patients with SSc, SLE, RA or SJS and healthy controls. (C) ROC curves for the predictive value of the SSc GRS to distinguish between patients with SLE, RA or SJS and patients with SSc. AUC, area under the ROC curves.

peripheral blood showed a significant contribution to the model, but the most significant contribution among the phenotypic variables corresponded to age (LRT p value=3.47×10^{-20}, online supplemental table 2).

When we combined only the informative variables into the same model, multivariate GLM, in addition to GRS and age, only 4 out of the 12 immune cell types remained as independently associated in the multivariate model: resting NK cells, M0 macrophages, activated dendritic cells and memory B cells (online supplemental table 3). The contribution of sex to the model did not remain significant when considering all the independent variables together and GRS score distributions between male and female patients did not show significant information (t-test p value=0.24, online supplemental table 3). Using leave-one-out prediction, we identified age as the most informative variable, followed by GRS (online supplemental table 4). We observed that the contribution of GRS to the model was comparable with the contribution of all significant parameters of immune cell count together (GRS LRT p value=2.59×10^{-12}; GRS LRT p value=1.26×10^{-12}, online supplemental table 4).

The multivariate GLM described above (SSc status ~GRS+Age+Memory B cells+Resting NK cells+M0 Macrophages+Activated dendritic cells) greatly outperformed the GRS and sex only model both in the initial (AUC discovery=0.847, 95% CI 0.81 to 0.88, p value=1.10×10^{-90}) and in the testing set (AUC=0.787, 95% CI 0.73 to 0.84, p value=1.31×10^{-24}),

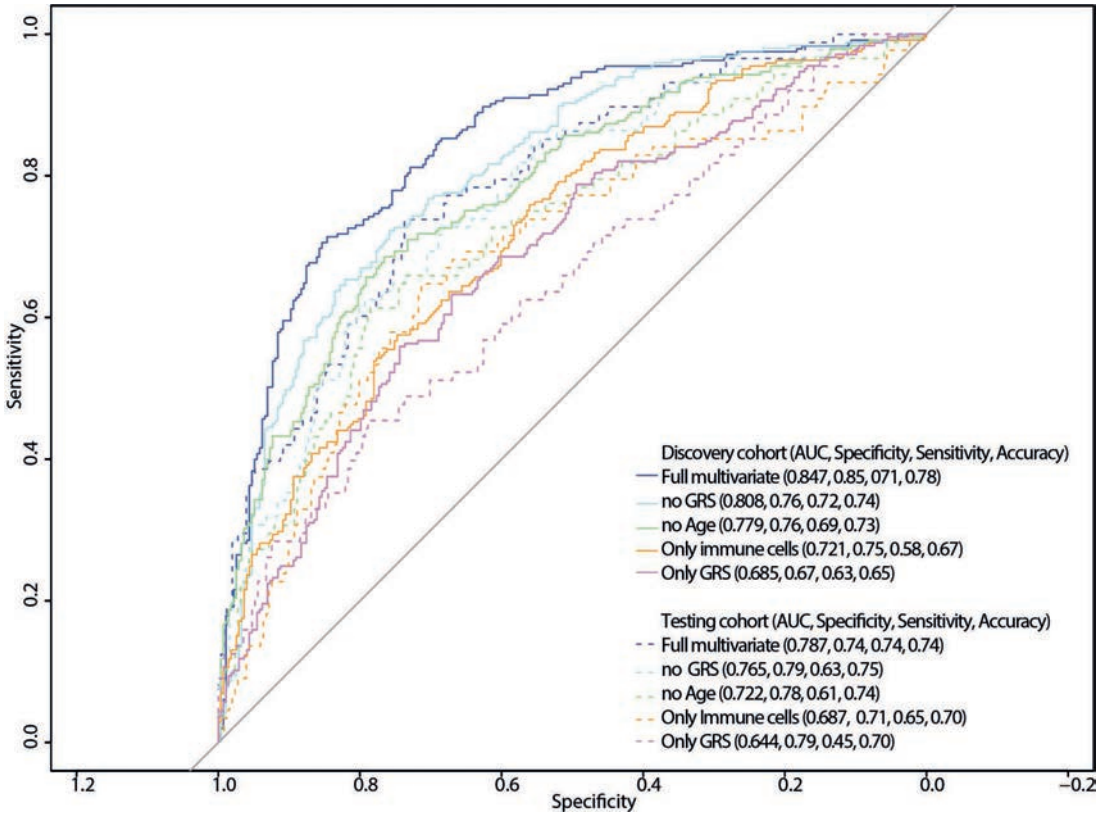

Figure 5 Receiver operating characteristic (ROC) curves for the predictive value of the multivariate generalised linear model (GLM), (SSc status ~GRS+Age+Memory B cells+Resting NK cells+M0 Macrophages+Activated dendritic cells) to distinguish between patients with SSc and healthy controls in the initial and replication cohorts depending on the variables included in the models. GRS, Genomic Risk Scores; NK cells, natural killer cells; SSc, systemic sclerosis.

as illustrated in figure 5. Moreover, the multivariate GLM outperformed the models that did not include age, GRS or both (figure 5).

DISCUSSION

We generated a GRS based on the allelic effects identified in the largest GWAS in SSc to date.[25] We obtained a predictive GRS model comprising 33 genetic polymorphisms, which allowed us to differentiate between SSc and controls in an independent SSc patient cohort.[27] A serological subtype-specific GRS (based on the GWAS comparison between ATA+ and ACA+ SSc patients) showed the best predictive value to classify patients based on the presence of different autoantibodies. Furthermore, we demonstrated the accuracy of the model in the differentiation between SSc and other IMIDs, such as RA and SJS. Finally, we complemented the SSc GRS with demographic data and peripheral blood immune cell counts in a multivariate model which reached a very significant recall rate.

The reported SSc GRS showed good predictive value (AUC=0.673), in line with the GRS developed for other IMIDs. For example, a similar AUC was reported for inflammatory bowel disease with a GRS based on the allelic effects observed for 12 882 cases and 132 532 healthy controls (AUC=0.72[29]) and in SLE (AUCs ranging 0.62–0.78.[16 17] Moreover, Stahl *et al* implemented a Bayesian inference model in a GWAS that comprised 5 485 cases of RA and 22 609 healthy controls, and the model explained 18% of the total variance, which is comparable to the variance explained by our model (R^2=0.13).[30] We would like to note that the previously conducted GWAS comprised 9 095 SSc cases and 17 584 controls, and the SSc GRS was developed in an independent cohort of 400 patients with SSc and 571 non-affected controls recruited for the PRECISESADS project.[27] Since sample size is key in the identification of reliable genetic association signals and in the accurate estimation of allelic effects in GWAS,[6 7 31] the presented SSc GRS represents a robust model supported by substantial statistical power. Nevertheless, despite the promising results of the described SSc GRS, the sensitivity and specificity of the model are still far from clinical use and it will require the addition of extra information and/or the development of well-powered phenotype-specific GWAS to identify cases with specific phenotypes with higher statistical power.

Furthermore, we consider that the SSc GRS is not heavily influenced by LD clumping, since we included only the top HLA SNP association in the GRS in order to avoid an over-representation of HLA polymorphisms without discarding completely the potential of this region in GRS. Nevertheless, it should be noted that all the samples included in the GWAS summary stats and in the score development cohorts for the SSc GRS had European ancestry[25 27] (online supplemental figure 1). One of the major limitations of GRS implementation is the bias toward populations with a similar ethnic origin to the discovery sample, that is, the GRS shows better accuracy in closely related populations.[7 32] As we illustrated in online supplemental figure 2, we found differences in the AUCs reached by the SSc GRS in the score development cohort depending on the origin of the individuals. Consequently, the performance of the SSc GRS in non-European or mixed populations should be taken with caution.[7 33]

A possible confounding factor for GRS in IMIDs is the shared genetic and immunological component that makes diagnosis complex and a slow clinical process especially in the early stages of these diseases.[34–36] As a clinical tool, a robust GRS improves

early diagnosis and helps in differential diagnosis.[31] Although the accuracy of the SSc GRS in differentiating between SSc and other IMIDs is still far from clinical standards, the model was able to discriminate between SSc and RA in 56.8% of the cases, and between SSc and SJS in 58.5% of the cases (figure 4). However, for SLE and SSc, which have a well-documented shared genetic component,[3 35] it was not possible to reach an accuracy that allowed for case differentiation. Taking into account the above, we consider that the reported GRS could enhance SSc diagnosis in the future and may contribute to personalised medicine, as a tool to assist physicians in the diagnosis of SSc.

In addition to comorbidities with other IMIDs, there is great variability in the disease course followed by patients with SSc, since their treatment and prognosis in the long term is very heterogeneous.[20] Chen *et al*[17] developed a GRS based on a GWAS analysing patients with SLE with and without renal involvement, but this SLE nephritis-specific GRS did not outperform the SLE severity predictions achieved with a SLE GRS. Following a similar strategy, we generated two additional GRS based on the GWAS comparisons between clinical and serological subtypes in patients with SSc. Remarkably, we showed that the serological subtype-specific GRS was able to differentiate SSc cases within the serological subtypes (ACA+ or ATA+), which is a promising result in the use of GRS to predict prognosis in SSc.[37] Regarding specific clinical outcomes, we focused on the use of GRS to predict lung fibrosis due to the disastrous effect of lung involvement on the survival of patients with SSc. We could not use SSc lung involvement GWAS data, but we observed that the serological subtype-specific GRS allowed us to correctly infer the existence of lung fibrosis on patients with SSc in 57.5% of cases (online supplemental figure 3).

Finally, we explored the possibilities of combining GRS with demographic and immunological covariates. We found that, out of all the covariates tested, age and the relative abundance of different immune cell types proved to be informative and resulted in a higher sensitivity in the case/control classification. As expected, age was confirmed as a very relevant factor in our model. Age is known to influence SSc, since patients with SSc are often diagnosed in their midlife ages.[19 38] On the other hand, sex was included as a covariate to calculate the best p value threshold for the GRS and in the multivariate model, but, in both cases, it was not very informative. This lack of significant contribution of sex to the GRS model was also reported previously in SLE.[17] Therefore, these counterintuitive results for a known SSc risk factor[19] were likely due to the selection of a sex-matched control population (online supplemental table 1), which would rule out the relevance of this parameter. The immune cell types included in the multivariate GRS were also concordant with the known aetiopathogenesis of the disease.[22] Functional defects or genetic susceptibility variants located in relevant genes for dendritic cells, macrophages and B cells have been described in patients with SSc.[39–43] T cell subtypes were relevant covariates in the model initially, but no T cell subset was selected for the multivariate model (online supplemental tables 2–4). Considering the central role of T cells in SSc, we hypothesise that since we could not include the Th1, Th2 or Th17 fractions in the model, this effect might have been overlooked.[43]

We have generated a GRS using a GWAS dataset and a score development cohort in which training was carried out and empirical p values for the GRS were obtained via permutation. Therefore, although both cohorts were independent, out-of-sample prediction has not been performed and it is a limitation of the present study. Consequently, our model and results should be considered as seminal work for future validation in additional cohorts of patients with SSc.

In summary, we developed a GRS based on the largest GWAS in SSc, resulting in a sensitive model to differentiate between SSc cases and non-affected controls, but also to differentiate within the different SSc serological subtypes (ATA+ and ACA+). Additionally, the GRS was also useful to differentiate patients with SSc from those affected by RA and SJS. We have shown that the GRS strategy in SSc has great potential to contribute to the field. However, several limitations and challenges, such as non-European ancestry or sample size, must be overcome to implement this strategy in clinical management.

Author affiliations
[1]Departamento de Genética e Instituto de Biotecnología, Universidad de Granada, Granada, Andalucía, Spain
[2]Instituto de Parasitologia y Biomedicina Lopez-Neyra, Granada, Andalucía, Spain
[3]Departament of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Catalunya, Spain
[4]Departament of Internal Medicine, Hospital Universitario San Cecilio, Granada, Andalucía, Spain
[5]Division of Rheumatology and Clinical Immunogenetics, University of Texas Health Science Center at Houston, Houston, Texas, USA
[6]Department of Dermatology, University of Cologne, Koln, Nordrhein-Westfalen, Germany
[7]Istituto di Clinica Medica Generale, Ematologia ed Immunologia Clinica, Università Politecnica delle Marche, Ancona, Marche, Italy
[8]Rheumatology, Leiden University Medical Center, Leiden, Zuid-Holland, Netherlands
[9]Rheumatology A Department, Hospital Cochin, Paris, Île-de-France, France
[10]Centre for Rheumatology, Royal Free and University College Medical School, London, UK
[11]Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, Utrecht, Netherlands
[12]Centre for Genomics and Oncological Research (GENYO), Pfizer-University of Granada-Andalusian Regional Government, Granada, Spain
[13]Scleroderma Unit, Referral Center for Systemic Autoimmune Diseases, La Fondazione IRCCS Ca' Granda Ospedale Maggiore di Milano Policlinico, Milano, Lombardia, Italy

Twitter Shervin Assassi @ShervinAssassi

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Collaborators International SSc Group: P. Carreira, Department of Rheumatology, 12 de Octubre University Hospital, Madrid, Spain; I. Castellvi, Department of Rheumatology, Santa Creu i Sant Pau University Hospital, Barcelona, Spain; R. Ríos, Department of Internal Medicine, San Cecilio Clinic University Hospital, Granada, Spain; J. L. Callejas, Department of Internal Medicine, San Cecilio Clinic University Hospital, Granada, Spain; R. García Portales, Department of Rheumatology, Virgen de la Victoria Hospital, Málaga, Spain; A. Fernández-Nebro, Department of Rheumatology, Carlos Haya Hospital, Málaga, Spain; F. J. García-Hernández, Department of Internal Medicine, Virgen del Rocío Hospital, Sevilla, Spain; M. A. Aguirre, Department of Rheumatology, Reina Sofía/IMIBIC Hospital, Córdoba, Spain; B. Fernández-Gutiérrez, Department of Rheumatology, San Carlos Clinic Hospital, Madrid, Spain; L. Rodríguez-Rodríguez, Department of Rheumatology, San Carlos Clinic Hospital, Madrid, Spain; P. García de la Peña, Department of Rheumatology, Madrid Norte Sanchinarro Hospital, Madrid, Spain; E. Vicente, Department of Rheumatology, La Princesa Hospital, Madrid, Spain; J. L. Andreu, Department of Rheumatology, Puerta de Hierro Hospital-Majadahonda, Madrid, Spain; M. Fernández de Castro, Department of Rheumatology, Puerta de Hierro Hospital-Majadahonda, Madrid, Spain; F. J. López-Longo, Department of Rheumatology, Gregorio Marañón University Hospital, Madrid, Spain; V. Fonollosa, Department of Internal Medicine, Valle de Hebrón Hospital, Barcelona, Spain; A. Guillén, Department of Internal Medicine, Valle de Hebrón Hospital, Barcelona, Spain; G. Espinosa, Department of Internal Medicine, Clinic Hospital, Barcelona, Spain; C. Tolosa, Department of Internal Medicine, Parc Tauli Hospital, Sabadell, Spain; A. Pros, Department of Rheumatology, Hospital Del Mar, Barcelona, Spain; M. Rodríguez Carballeira, Department of Internal Medicine, Hospital Universitari Mútua Terrasa, Barcelona, Spain; F. J. Narváez, Department of Rheumatology, Bellvitge University Hospital, Barcelona, Spain; M. Rubio Riva, Department of Internal Medicine, Bellvitge University Hospital, Barcelona, Spain; V. Ortiz-Santamaría, Department of Rheumatology, Granollers Hospital, Granollers, Spain; A. B. Madroñero, Department of Internal Medicine, Hospital General San Jorge, Huesca, Spain; M. A. González-Gay, Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, DIVAL, University of Cantabria, Santander, Spain; B. Díaz,

Department of Internal Medicine, Hospital Central de Asturias, Oviedo, Spain; L. Trapiella, Department of Internal Medicine, Hospital Central de Asturias, Oviedo, Spain; M. V. Egurbide, Department of Internal Medicine, Hospital Universitario Cruces, Barakaldo, Spain; P. Fanlo-Mateo, Department of Internal Medicine, Hospital Virgen del Camino, Pamplona, Spain; L. Saez-Comet, Department of Internal Medicine, Hospital Universitario Miguel Servet, Zaragoza, Spain; F. Díaz, Department of Rheumatology, Hospital Universitario de Canarias, Tenerife, Spain; E. Beltrán, Department of Rheumatology, Hospital General Universitario de Valencia, Valencia, Spain; J. A. Roman-Ivorra, Department of Rheumatology, Hospital Universitari i Politecnic La Fe, Valencia, Spain; J. J. Alegre Sancho, Department of Rheumatology, Hospital Universitari Doctor Peset, Valencia, Spain; M. Freire, Department of Internal Medicine, Thrombosis and Vasculitis Unit, Complexo Hospitalario Universitario de Vigo, Vigo, Spain; F. J. Blanco Garcia, Department of Rheumatology, INIBIC-Hospital Universitario A Coruña, La Coruña, Spain; N. Oreiro, Department of Rheumatology, INIBIC-Hospital Universitario A Coruña, La Coruña, Spain; T. Witte, Department of Clinical Immunology, Hannover Medical School, Hannover, Germany; A. Kreuter, Department of Dermatology, Josefs-Hospital, Ruhr University Bochum, Bochum, Germany; G. Riemekasten, Clinic of Rheumatology, University of Lübeck, Lübeck, Germany; P. Airo, Service of Rheumatology and Clinic Immunology Spedali Civili, Brescia, Italy; C. Magro, Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands; A. E. Voskuyl, Department of Rheumatology, VU University Medical Center, Amsterdam, The Netherlands; M. C. Vonk, Department of Rheumatology, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands; R. Hesselstrand, Department of Rheumatology, Lund University, Lund, Sweden; A. Nordin, Division of Rheumatology, Department of Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden; A. L. Herrick, Centre for Musculoskeletal Research, The University of Manchester, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK, NIHR Manchester Biomedical Research Centre, Manchester, UK; C. Lunardi, Department of Medicine, Università degli Studi di Verona, Verona, Italy; G. Moroncini, Clinica Medica, Department of Clinical and Molecular Science, Università Politecnica delle Marche and Ospedali Riuniti, Ancona, Italy; A. Hoffmann-Vold, Department of Rheumatology, Oslo University Hospital, Oslo, Norway; J. H. W. Distler, Department of Internal Medicine 3, Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany; L. Padyukov, Division of Rheumatology, Department of Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden; B. P. C. Koeleman, University Medical Center Utrecht, Utrecht, The Netherlands. Australian Scleroderma Interest Group (ASIG): J. Zochling, Menzies Research Institute Tasmania, University of Tasmania, Hobart, TAS, Australia; J. Sahhar, Department Rheumatology, Monash Medical Centre, Melbourne, VIC, Australia; J. Roddy, Rheumatology, Royal Perth Hospital, Perth, WA, Australia; P. Nash, Research Unit, Sunshine Coast Rheumatology, Maroochydore, QLD, Australia; K. Tymms, Canberra Rheumatology, Canberra, ACT, Australia; M. Rischmueller, Department Rheumatology, The Queen Elizabeth Hospital,Woodville, SA, Australia; S. Lester, Department Rheumatology, The Queen Elizabeth Hospital, Woodville, SA, Australia; S. Proudman, Royal Adelaide Hospital and University of Adelaide, Adelaide, SA, Australia; W. Stevens, St. Vincent's Hospital, Melbourne, VIC, Australia; M. Nikpour, The University of Melbourne at St. Vincent's Hospital, Melbourne, VIC, Australia; M. A. Brown, Institute of Health and Biomedical Innovation, Queensland University of Technology,Translational Research Institute, Princess Alexandra Hospital, Brisbane, QLD, Australia. PRECISESADS Clinical Consortium: Doreen Belz, Klinik und Poliklinik für Dermatologie und Venerologie, Uniklinik Köln, Köln, Germany; Francesca Ingegnoli, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; Yolanda Jimenez Gómez, IMIBIC, Reina Sofia Hospital, University of Cordoba, Cordoba, Spain; Chary Lopez Pedrera, IMIBIC, Reina Sofia Hospital, University of Cordoba, Cordoba, Spain; Rik Lories, Division of Rheumatology, University Hospitals Leuven and Skeletal Biology and Engineering Research Center, KU Leuven, Leuven, Belgium; Eduardo Collantes-Estevez, IMIBIC, Reina Sofia Hospital, University of Cordoba, Cordoba, Spain; Gaia Montanelli, Scleroderma Unit, Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy; Silvia Piantoni, Immunology & Allergy, University Hospital and School of Medicine, Geneva, Switzerland; Ignasi Rodriguez Pinto, Division of Rheumatology, University Hospitals Leuven and Skeletal Biology and Engineering Research Center, KU Leuven, Leuven, Belgium; Carlos Vasconcelos, Serviço de Imunologia EX-CICAP, Centro Hospitalar e Universitário do Porto, Porto, Portugal. PRECISESADS Flow Cytometry study group: Christophe Jamin, 1U1238, Université de Brest, Inserm, Labex IGO, CHU de Brest, Brest, France; Concepción Marañón, GENYO, Centre for Genomics and Oncological Research Pfizer, University of Granada, Andalusian Regional Government, PTS GRANADA, Granada, Spain; Lucas Le Lann, 1U1238, Université de Brest, Inserm, Labex IGO, CHU de Brest, Brest, France; Quentin Simon, 1U1238, Université de Brest, Inserm, Labex IGO, CHU de Brest, Brest, France; Bénédicte Rouvière, 1U1238, Université de Brest, Inserm, Labex IGO, CHU de Brest, Brest, France; Nieves Varela, GENYO, Centre for Genomics and Oncological Research Pfizer, University of Granada, Andalusian Regional Government, PTS GRANADA, Granada, Spain; Brian Muchmore, GENYO, Centre for Genomics and Oncological Research Pfizer, University of Granada, Andalusian Regional Government, PTS GRANADA, Granada, Spain; Aleksandra Dufour, Immunology & Allergy, University Hospital and School of Medicine, Geneva, Switzerland; Montserrat Alvarez, Immunology & Allergy, University Hospital and School of Medicine, Geneva, Switzerland; Jonathan Cremer, Laboratory of Clinical Immunology, Department of Microbiology and Immunology, KU Leuven, Leuven, Belgium; Nuria Barbarroja, IMIBIC, Reina Sofia Hospital, University of Cordoba, Cordoba, Spain; Velia Gerl, Department of Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, Germany; Laleh Khodadadi, Department of Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, Germany; Qingyu Cheng, Department of Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, Germany; Anne Buttgereit, Bayer AG, Berlin, Germany; Aurélie De Groof, Pôle de Pathologies Rhumatismales Inflammatoires et Systémiques, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium; Julie Ducreux, Pôle de Pathologies Rhumatismales Inflammatoires et Systémiques, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium; Elena Trombetta, Laboratorio di Analisi Chimico Cliniche e Microbiologia - Servizio di Citofluorimetria, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milano, Italy; Tianlu Li, Chromatin and Disease Group, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain; Damiana Alvarez-Errico, Chromatin and Disease Group, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain; Torsten Witte, Klinik für Immunologie und Rheumatologie, Medical University Hannover, Hannover, Germany; Katja Kniesch, Klinik für Immunologie und Rheumatologie, Medical University Hannover, Hannover, Germany; Nancy Azevedo, GENYO, Centre for Genomics and Oncological Research Pfizer, University of Granada, Andalusian Regional Government, PTS GRANADA, Granada, Spain; Esmeralda Neves, GENYO, Centre for Genomics and Oncological Research Pfizer, University of Granada, Andalusian Regional Government, PTS GRANADA, Granada, Spain; Nancy Azevedo, IMIBIC, Reina Sofia Hospital, University of Cordoba, Cordoba, Spain and Serviço de Imunologia EX-CICAP, Centro Hospitalar e Universitário do Porto, Porto, Portugal; Esmeralda Neves, IMIBIC, Reina Sofia Hospital, University of Cordoba, Cordoba, Spain and Serviço de Imunologia EX-CICAP, Centro Hospitalar e Universitário do Porto, Porto, Portugal; Sambasiva Rao, Sanofi Genzyme, Framingham, MA, USA; Pierre-Emmanuel Jouve, AltraBio SAS, Lyon, France.

Contributors LB-C: data analysis, manuscript drafting, revision and approval; GV-M: data analysis, manuscript drafting, revision and approval; MK: interpretation of data, manuscript revision and approval; MA-H: interpretation of data, manuscript revision and approval; ELI: data interpretation, manuscript revision and approval; PRECISESADS Clinical Consortium: data acquisition, manuscript revision and approval; MEAI-R: data interpretation, manuscript revision and approval; LB: data interpretation, manuscript revision and approval; JM: study design, manuscript drafting, revision and approval.

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Patient consent for publication Not required.

Ethics approval An ethical protocol was prepared, consensus was reached across all partners, academic and industrial, translated into all participants' languages and approved by each of the local ethical committees of the clinical recruitment centres. The studies adhered to the standards set by the International Conference on Harmonization and Good Clinical Practice (ICH-GCP), and to the ethical principles that have their origin in the Declaration of Helsinki (2013). The protection of the confidentiality of records that could identify the included subjects is ensured as defined by the EU Directive 2001/20/EC and the applicable national and international requirements relating to data protection in each participating country. The CS study is registered with number NCT02890121, and the inception study with number NCT02890134 in ClinicalTrials.gov. The study (PRECISESADS cross-sectional study) was approved by the following ethic committees: Comitato Etico Area 2 (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano and University of Milan); approval no. 425bis 19 November 2014, and no. 671_2018 19 September 2018; Klinikum der Universitaet zu Koeln, Cologne, Germany. Geschaftsstelle Ethikkommission; Pôle de pathologies rhumatismales systémiques et inflammatoires, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium. Comité d Èthique Hospitalo-Facultaire; University of Szeged, Szeged, Hungary. Csongrad Megyei Kormanyhivatal; Hospital

Clinic I Provicia, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain. Comité de Ética de Investigación Clínica del Hospital Clínic de Barcelona. Hospital Clinic del Barcelona; Servicio Andaluz de Salud, Hospital Universitario Reina Sofía Córdoba, Spain. Comité de Ética de la Investigación de Centro de Granada (CEI – Granada); Centro Hospitalar do Porto, Portugal. Comissao de ética para a Saude – CES do CHP; Centre Hospitalier Universitaire de Brest, Hospital de la Cavale Blanche, Avenue Tanguy Prigent 29609, Brest, France. Comité de Protection des Personnes Ouest VI; Hôpitaux Universitaires de Genève, Switzerland. DEAS –Commission Cantonale d'éthique de la recherche Hôpitaux Universitaires de Genève; Biobanco del Sistema Sanitario Público de Andalucía, Granada, Spain; Katholieke Universiteit Leuven, Belgium. Commissie Medische Ethiek UZ KU Leuven /Onderzoek; Charite, Berlin, Germany. Ethikkommission; Medizinische Hochschule Hannover, Germany. Ethikkommission.

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ORCID iDs
Gonzalo Villanueva-Martin http://orcid.org/0000-0002-3585-4319
Shervin Assassi http://orcid.org/0000-0002-8059-9978
Yannick Allanore http://orcid.org/0000-0002-6149-0002
Christopher P Denton http://orcid.org/0000-0003-3975-8938
Lorenzo Beretta http://orcid.org/0000-0002-6529-6258

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TRANSLATIONAL SCIENCE

Fast diagnostic test for familial Mediterranean fever based on a kinase inhibitor

Flora Magnotti,[1] Tiphaine Malsot,[1] Sophie Georgin-lavialle ,[2,3] Fatima Abbas,[4] Amandine Martin,[1] Alexandre Belot ,[1,3,5] Maxime Fauter,[6,7] Muriel Rabilloud,[4] Mathieu Gerfaud-Valentin,[6] Pascal Sève,[6] Agnes Duquesne,[5] Arnaud Hot,[8] Stephane Durupt,[9] Léa Savey,[2] Irina Giurgea,[10] Gilles Grateau,[2,3] Thomas Henry,[1] Yvan Jamilloux [1,6]

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For numbered affiliations see end of article.

Correspondence to
Yvan Jamilloux, Internal Medicine, Hospices Civils de Lyon, Lyon 69002, France; yvan.jamilloux@chu-lyon.fr

TH and YJ are joint senior authors.

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ABSTRACT

Background and objective Familial Mediterranean fever (FMF) is the most frequent hereditary autoinflammatory disease. Its diagnosis relies on a set of clinical criteria and a genetic confirmation on identification of biallelic pathogenic *MEFV* variants. *MEFV* encodes pyrin, an inflammasome sensor. Using a kinase inhibitor, UCN-01, we recently identified that dephosphorylation of FMF-associated pyrin mutants leads to inflammasome activation. The aim of this study was to assess whether quantifying UCN-01-mediated inflammasome activation could discriminate FMF patients from healthy donors (HD) and from patients with other inflammatory disorders (OID).

Methods Real-time pyroptosis and IL-1β secretion were monitored in response to UCN-01 in monocytes from FMF patients (n=67), HD (n=71) and OID patients (n=40). Sensitivity and specificity of the resulting diagnostic tests were determined by receiver operating characteristic curve analyses.

Results Inflammasome monitoring in response to UCN-01 discriminates FMF patients from other individuals. Pyroptosis assessment leads to a fast FMF diagnosis while combining pyroptosis and IL-1β dosage renders UCN-01-based assays highly sensitive and specific. UCN-01-triggered monocytes responses were influenced by *MEFV* gene dosage and *MEFV* mutations in a similar way as clinical phenotypes are.

Conclusions UCN-01-based inflammasome assays could be used to rapidly diagnose FMF, with high sensitivity and specificity.

Key messages

What is already known about this subject?

- Genetic analysis of the *MEFV* gene is often inconclusive due to the large number of variants of uncertain significance.

What does this study add?

- Monitoring pyroptosis in real time allows a fast diagnosis of patients with familial Mediterranean fever (FMF).
- Monitoring both cell-death kinetics and IL-1β release accurately discriminates patients with FMF from other patients.
- The nature and the number of the *MEFV* variants influence the degree of in vitro activation of the pyrin inflammasome.

How might this impact on clinical practice or future developments?

- The test could guide early clinical decisions and management by identifying FMF patients who will require colchicine and genetic analyses while others (the negative ones) will need deeper investigations including the search for alternative diagnosis.

INTRODUCTION

Familial Mediterranean fever (FMF) is an inherited autoinflammatory syndrome present worldwide as a rare disease.[1] A high prevalence (up to 1/500) is observed in the Mediterranean basin.[2] FMF is characterised by recurrent attacks of fever and serositis, associated with systemic inflammation. The major challenge of FMF is to establish a fast and definitive diagnosis, to avoid unnecessary and costly investigations, prolonged diagnostic wandering or useless life-long treatment.[3]

FMF diagnosis results from a combination of clinical criteria,[4] and is confirmed when biallelic mutations in *MEFV*, the gene encoding pyrin, are observed.[5 6] Yet, genetic tests may be inconclusive, about one-third of patients bearing only one mutated *MEFV* allele.[7] Genetic analyses can also reveal variants of uncertain significance.[8] Therefore, it is of great importance to develop a rapid diagnostic test.

Recently, using a kinase inhibitor, UCN-01, we demonstrated that pyrin dephosphorylation triggers full inflammasome activation in FMF monocytes while it does not in healthy donor (HD) monocytes.[9] We hypothesised that these differential responses could be the basis of a diagnostic test to quickly distinguish FMF patients from HD or patients suffering from other inflammatory disorders (OID).

METHODS

Methods are detailed in the supplementary material.

The study was approved by the *Comité de Protection des Personnes* (#2018/95). Every participant

(online supplemental table 1) gave informed consent. Statistical analysis was performed with R software.

RESULTS

Cell death kinetics discriminates FMF patients from HD and patients with OID

Pyroptosis was monitored in real time in monocytes from FMF patients bearing homozygous p.M694V or p.M694I mutations, HD and controls with OID. UCN-01 triggered a rapid cell death in FMF monocytes while a late cell death was observed in monocytes from HD or OID (figure 1A). The difference in cell death kinetics was highly significant as determined by quantifying the areas under the curve ($p<0.0001$; figure 1B) and by comparing the UCN-01-incubation time leading to 20% of cell death ($p<0.0001$; figure 1C). Receiver operating characteristic (ROC) curves and regression analysis established that monitoring cell death during 60 min of UCN-01 treatment discriminated FMF patients from HD with a sensitivity of 95.7% and a specificity of 94.7% (figure 1D).

When applied to a cohort of OID patients, the same analysis accurately classified 94.9% of the patients. Thus, monitoring UCN-01-triggered pyroptosis discriminates FMF patients from other patients with a sensitivity of 92.1% and a specificity of 97.5% (figure 1E).

Importantly, this experiment does not require an LPS priming step, providing results 1 hour postmonocyte isolation.

Biparametric analyses increase the sensitivity and specificity of the test

We then wondered whether a biparametric test, based also on IL-1β quantification, could better discriminate the different patient groups.

Following lipopolysaccharide (LPS) priming and pyrin activation, mean IL-1β levels in monocyte supernatants were 15-fold higher in homozygous FMF patients (1521±1168 pg/mL) than in HD (92.7±111 pg/mL; $p<0.0001$) or patients with OID (99.16±108 pg/mL; $p<0.0001$) (figure 2A). The discrimination threshold between these FMF patients and HD was determined at 260.6 pg/mL, giving a sensitivity of 97.1% and a specificity of 91.2% (figure 2B).

Similar results were obtained when applying this analysis to a cohort of patients with OID (100% sensitivity and 97.3% specificity; figure 2C). Thus, IL-1β dosage following UCN-01 treatment discriminates FMF patients from HD and patients with OID.

Importantly, by combining the two parameters, homozygous FMF patients were fully segregated from HD ($p<0.0001$), while one patient in the OID group was classified as a false positive ($p<0.0001$) (figure 2D). Of note, the *MEFV* genotype of this patient with Behçet's disease is unknown and we cannot exclude that he is carrying a pathogenic *MEFV* variant (more prevalent in patients with Behçet's disease than in an ethnically matched population).[10 11]

Hence, monitoring both pyroptosis and IL-1β strengthens the discriminating power of the assay (sensitivity of 100% and specificity of 99%; figure 2 and F).

Gene dosage determines UCN-01-mediated responses

MEFV-gene dosage plays an important role in the phenotype of FMF.[12 13] We therefore wondered whether cellular responses to UCN-01 were influenced by gene dosage in the same way as the clinical phenotype. Patients with monoallelic (n=10) or biallelic (n=38) variants at the p.M694 residue were selected for this analysis. Real-time pyroptosis monitoring identified significant differences between heterozygous and homozygous patients ($p=0.0015$; figure 3A and B). Furthermore, monocytes from heterozygous patients released significantly less IL-1β than

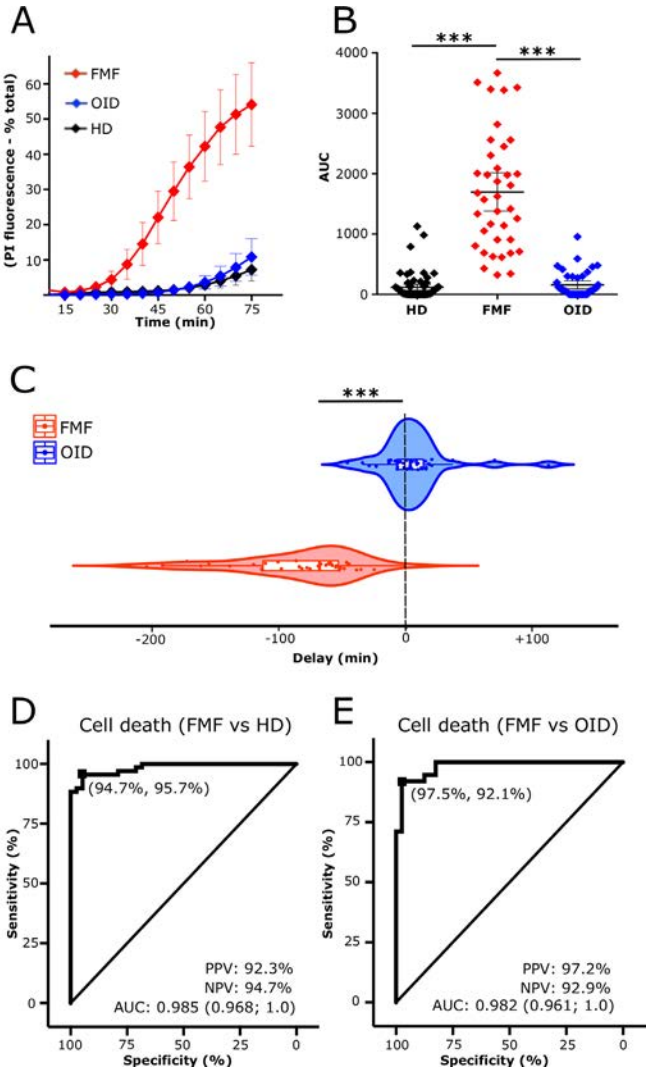

Figure 1 Protein Kinase C (PKC) inhibitors trigger a fast cell death specifically in monocytes from FMF patients. (A–C) Monocytes from HD (n=71), FMF patients bearing biallelic p.M694I/V variants (n=38) or patients with OID (n=40) were treated with 12.5 µM UCN-01. (A) Cell death was monitored in real time by measuring propidium iodide (PI) influx every 5 min. (B) The areas under the curve (AUC) were computed for each patient after 60 min of UCN-01 treatment. (C) The time required to reach 20% cell death was calculated for each HD, FMF and patients with OID. The values were normalised by subtracting the result obtained for the HD with the value obtained for the FMF/OID analysed at the same time. (D and E) Receiver operating characteristic (ROC) curves were computed for the area under the cell death kinetics curve following UCN-01 treatment by comparing HD with FMF (D) and FMF with OID patients (E). For each ROC curve, the AUC, specificity, sensitivity, as well as the positive predictive value (PPV) and the negative predictive value (NPV) are indicated. Data information: (A) each point of the curve corresponds to the average of the mean cell death values from three biological replicates of monocytes from the indicated patients. (B and C) Each dot represents the value from one patient. (A and B) The bar represents the 95% CI. ***$p<0.001$ by Mann-Whitney rank-sum test. FMF, familial Mediterranean fever; HD, healthy donors; OID, other inflammatory disorders.

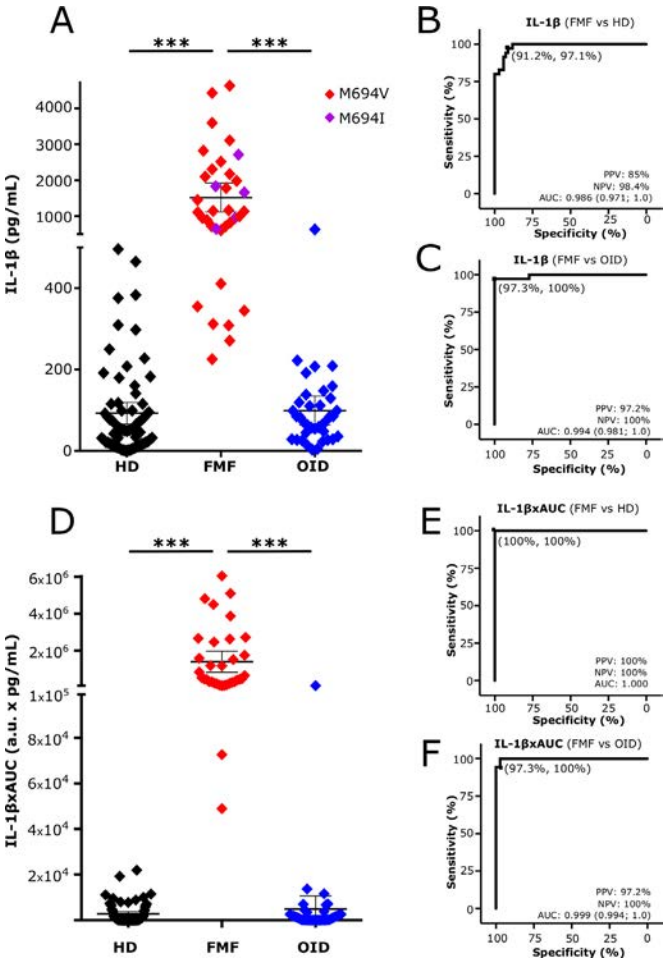

Figure 2 Biparametric analysis discriminates FMF patients from HD or OID. (A) Monocytes from HD (n=71), FMF bearing biallelic p.M694I/V variants (n=35), and patients with OID (n=39) were primed with LPS during 3 hour and treated with 12.5 µM UCN-01 for 1.5 hour. IL-1β levels in monocyte supernatants were quantified by ELISA. (B and C) ROC curves were computed for the obtained IL-1β values by comparing FMF and HD (B) and FMF and patients with OID (C). (D) Cell death data and IL-1β data were combined by multiplying the mean area under the cell death kinetics curve by the concentrations of IL-1β for each patient. The log value is represented in the figure. (E and F) ROC curves were computed for the biparametric analysis data by comparing FMF and HD (E) and FMF and patients with OID (F). For each ROC curve, the AUC, specificity, sensitivity, as well as the positive predictive value (PPV) and the negative predictive value (NPV) are indicated. Data information: (A, D) each dot represents the mean value from three biological replicates for one patient (A) or the calculated value from one patient (D). (A, D) The bar represents the 95% CI. ***p<0.001 by Mann-Whitney rank-sum test. AUC, areas under the curve; FMF, familial Mediterranean fever; HD, healthy donors; OID, other inflammatory disorders; ROC, receiver operating characteristic.

monocytes from homozygous patients did (p=0.024; figure 3C). Biparametric analyses confirmed the gene dosage effect by demonstrating a significant difference between monocytes carrying monoallelic versus biallelic *MEFV* variants (p=0.0044; figure 3D).

Importantly, heterozygous FMF patients were also discriminated from HD using UCN-01-based assays (p<0.001; figure 3A–C and online supplemental figure 1). Colchicine treatment did not impact the test (online supplemental figure 2).

Altogether, these results demonstrate a gene dosage impact on the UCN-01-triggered responses and show that UCN-01-based functional assays segregate homozygous or heterozygous FMF patients from HD. Interestingly, these results are highly consistent with the impact of the *MEFV* gene dosage on clinical phenotypes.[12]

MEFV genotype influences monocyte responses to UCN-01

374 *MEFV* variants are listed in the Infevers registry and the pathogenicity of most of them is unclear.[8 14] We thus investigated the responses of monocytes from FMF patients with homozygous mutations not located at the p.M694 site. Three patients with homozygous mutations (p.M680I, p.V726A and p.P369S) were analysed (online supplemental figure 3A-D). Although caution must be raised due to the inclusion of a single patient per genotype, a gradient of UCN-01-triggered responses was observed which is highly consistent with the described impact of the corresponding mutations on clinical phenotypes.[15–17] The impact of genotypes on in vitro phenotypes could be classified as follows p.M694V/I>p.M680I>p.V726A>p.P369S

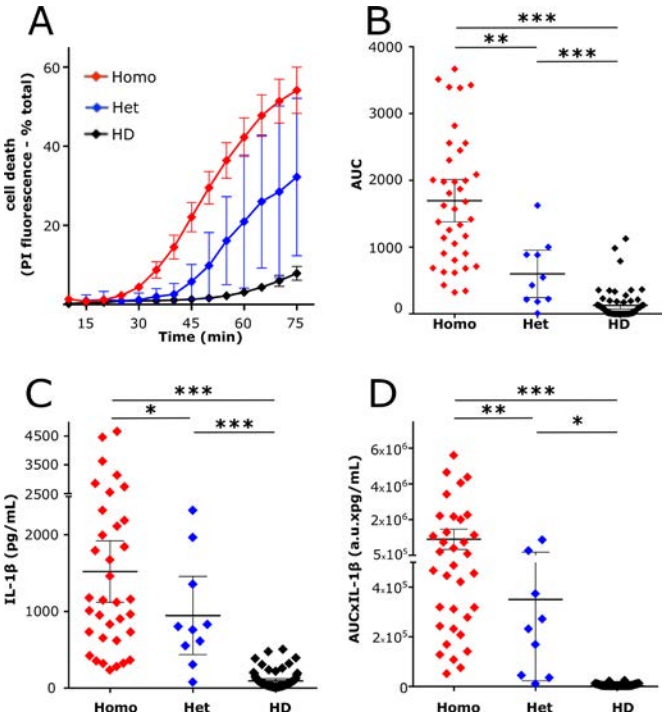

Figure 3 UCN-01 treatment discriminates FMF heterozygous patients who present a gene dosage response. Monocytes from HD (n=71), FMF homozygous (p.M694I-V/p.M694I-V) patients (Homo, n=38) and FMF heterozygous (p.M694I-V/0) patients (Het, n=10) were treated with 12.5 µM UCN-01 after LPS priming (C) or not (A). (A) Cell death was monitored in real time by measuring propidium iodide influx every 5 min. (B) The AUC were computed for each patient after 60 min of UCN-01 treatment. (C) IL-1β levels in monocyte supernatants were quantified by ELISA. (D) The two parameters were combined by multiplying the mean AUC by the concentration of IL-1β obtained for each patient. Data information: (A) each point of the curve corresponds to the average of the mean cell death values from three biological replicates of monocytes from the indicated patients. (B–D) Each dot represents the value from one patient. (C) Each dot represents the mean value from three biological replicates for one patient. (A–D) The bar represents the 95% CI. *p<0.05, **p<0.01, ***p<0.001 by Mann-Whitney rank-sum test. AUC, areas under the curve; FMF, familial Mediterranean fever; HD, healthy donors; ns, not significant.

which mirrors the clinical phenotype–genotype studies.[15–18] The biparametric analysis segregated the homozygous p.M680I and p.V726A patients from the HD, but not the FMF patient harbouring the p.P369S/P369S genotype (online supplemental figure 3D). Interestingly, p.P369S is a variant of uncertain significance which does not behave like typical FMF-associated *MEFV* variants, as observed in in vitro experiments on monocyte cell lines,[11] or in a recently developed colchicine-resistance assay.[19] These results suggest that the p.P369S variant is a non-pathogenic variant or that its pathogenicity is associated with another molecular mechanism.

Finally, we analysed the ability of UCN-01-based tests to discriminate compound heterozygous FMF patients from HD (online supplemental figure 3E-H). The in vitro responses of monocytes bearing two different *MEFV* variants were lower than in vitro responses of p.M694V/I homozygous monocytes. When combined with the clearly pathogenic p.M694 variants, mutations on the second *MEFV* allele impacted differentially the in vitro responses with a hierarchy (p.M680I, p.R761H>p.V726A and p.E148Q) largely mirroring the gradient of clinical phenotypes (from severe to mild) observed in FMF patients. Importantly, biparametric analyses discriminated also compound heterozygous FMF patients from HD with a sensitivity of 92.3% and a specificity of 100%.

DISCUSSION

Here, we demonstrate that a functional assay, based on kinase inhibition and monitoring of pyroptosis and IL-1β release, accurately diagnoses FMF over a large number of *MEFV* genotypes. This test discriminates FMF patients from HD and patients with OID, including patients with monogenic diseases (online supplemental figure 4). Besides the usual quantification of IL-1 release, the test takes advantage of the real-time analysis of pyroptosis, a hallmark of inflammasome activation.

The cell death assay brings results within 3 hours (2 hours for sample preparation + 1 hour for cell death kinetics) and costs less than 8€/sample (online supplemental table 2). Thus, it could be used in routine to support clinical findings. Due to its good positive predictive value, the test detects true positive FMF patients, for whom treatment could be initiated promptly, deep investigations re-evaluated and genetic confirmation reached. On the other hand, its good negative predictive value indicates a robust way to identify true negative patients, who require further investigations, reasoned genetic testing and postponed (or even no) colchicine initiation. Of note, biparametric analyses should be used whenever the test based on cell death leads to negative results in order to build confidence in the results.

Our test identifies FMF patients with monoallelic and biallelic *MEFV* mutations. These results are in line with clinical findings of patients with full-blown clinical FMF-bearing monoallelic *MEFV* mutations. Interestingly, and although the results need to be confirmed in larger cohorts, the in vitro monocyte responses to UCN-01 largely mimic clinical responses to colchicine[11 15] and the genotype–phenotype results.[10 14 16 17] However, one limitation stems from the fact that most FMF patients included in this study present at least one clearly pathogenic *MEFV* mutation (p.M694V/I, p.M680I and p.V726A). Confirmatory analyses on a larger cohort of patients are needed to better delineate the specificity of the UCN-01-based assay with regard to rare *MEFV* genotypes.

Our test uses isolated monocytes, preventing its transfer to routine laboratories in its current design. Nevertheless, we and others[19] have preliminary data indicating that functional assays in whole blood are feasible and reliable, at least for cytokine release assessment (online supplemental figure 5).

Altogether, functional assays are promising approaches for rapid detection of FMF patients with clearly pathogenic mutations.[19 20] Yet, the evaluation of pretest probability (ie, epidemiological and clinical data) remains the key in early decisions, thus positioning functional assays at the crossroads of clinics and genetics.

Author affiliations
[1]Centre International de Recherche en Infectiologie (CIRI), Inserm U1111, Université Claude Bernard-Lyon 1, CNRS, Ecole Normale Supérieure de Lyon, Lyon, France
[2]Internal Medicine, Tenon Hospital, AP-HP, Paris, France
[3]CEREMAIA (Centre de Référence des Maladies Autoinflammatoires et des Amyloses), Paris, France
[4]Biostatistics, Pôle de Santé Publique,CNRS UMR5308, Hospices Civils de Lyon, Lyon, France
[5]Department of Paediatric Nephrology, Rheumatology, Dermatology, Hôpital Femme-Mère Enfant, Université Claude Bernard-Lyon 1, Hospices Civils de Lyon, Bron, France
[6]Internal Medicine, University Hospital Croix-Rousse, Hospices Civils de Lyon, Lyon, France
[7]Internal Medicine, Hospices Civils de Lyon, Lyon, France
[8]Internal Medicine, University Hospital Edouard Herriot, Hospices Civils de Lyon, Lyon, France
[9]Internal Medicine, University Hospital Lyon Sud, Hospices Civils de Lyon, Lyon, France
[10]Genetics, Armand-Trousseau Hospital, APHP, Sorbonne University, Paris, Île-de-France, France

Twitter Sophie Georgin-lavialle @SophieGeorgin

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Contributors TH and YJ designed the study; FM, TM, AM, MF, TH performed experiments; FM, FA, MR, TH and YJ analysed the data. FM, TH and YJ wrote the manuscript with input from all authors; SG-L, AB, MG-V, PS, AD, AH, SD, GG and YJ included patients, provided clinical information and samples; TH and YJ oversaw the project.

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Competing interests YJ, FM, AB, AM and TH are coinventors and owners of a patent 'Methods and kits for diagnosis of familial Mediterranean fever' (WO/2019/048569).

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 required.

Ethics approval The study was approved by the French Comité de Protection des Personnes (CPP,#L16-189) and by the French Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS, #16.864). The experiments conformed to the principles set out in the WMA Declaration of Helsinki and the Department of Health and Human Services'Belmont Report. The Etablissement Français du Sang provided HD blood in the framework of the convention #14-1820. Informed consent was received from each participant prior to inclusion in the study.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Additional data are available upon reasonable request.

ORCID iDs
Sophie Georgin-lavialle http://orcid.org/0000-0001-6668-8854
Alexandre Belot http://orcid.org/0000-0003-4902-5332
Yvan Jamilloux http://orcid.org/0000-0001-5249-3650

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Age-based (<65 vs ≥65 years) incidence of infections and serious infections with tofacitinib versus biological DMARDs in rheumatoid arthritis clinical trials and the US Corrona RA registry

A randomised, open-label, blinded endpoint post-authorisation safety study (Study A3921133; NCT02092467; database not locked and subject to change) evaluated the safety of tofacitinib 5 mg and 10 mg twice daily (BID) versus tumour necrosis factor inhibitors (TNFi) (adalimumab/etanercept) in rheumatoid arthritis (RA) patients aged ≥50 years with ≥1 cardiovascular risk factor. An ad hoc interim safety analysis of Study A3921133 reported incidence rates (IRs) per 100 patient-years (95% CIs) for fatal infections (within 28 days of treatment) and non-fatal serious infection events (SIEs), respectively: tofacitinib 5 mg BID, 0.18 (0.07 to 0.39) and 3.35 (2.78 to 4.01); tofacitinib 10 mg BID, 0.22 (0.09 to 0.46) and 3.51 (2.93 to 4.16); TNFi, 0.06 (0.01 to 0.22) and 2.79 (2.28 to 3.39).[1] SIEs risk (fatal/non-fatal) was further increased with tofacitinib in patients aged >65 years versus younger patients; therefore, the European Medicines Agency recommended that older patients should receive tofacitinib when there is no suitable alternative treatment.[2]

Further to these recommendations, we sought to assess age-based (<65 vs ≥65 years) SIE risk in RA patients receiving tofacitinib in Phase 2, 3 and 3b/4 tofacitinib studies with a TNFi control/comparator arm,[3–5] and in the US Corrona RA registry.

The clinical data set included 2180 patients (tofacitinib 5 mg BID, n=1064 (943.4 patient-years); tofacitinib 10 mg BID, n=306 (236.6 patient-years); adalimumab, n=643 (554.3 patient-years); placebo, n=167 (108.1 patient-years)). Overall, 1841 (84.4%) patients were aged <65 years and 339 (15.6%) ≥65 years. Crude IRs (patients with events/100 patient-years) and HRs were calculated for all first infections and first SIEs, overall and by age.

For all infections (online supplemental figure S1), IRs and infection risk (by HRs) were higher with active treatments versus placebo, and similar across active treatments and age groups. For SIEs (figure 1), IRs were higher in older versus younger patients for active treatments, and similar among younger patients for all treatments. For older patients, versus adalimumab, SIE IRs were similar for tofacitinib 5 mg BID and numerically higher for tofacitinib 10 mg BID, though few events occurred in this group (n=4), and the HR 95% CI was wide and included 1. Importantly, HRs revealed similar SIE risk between older and younger patients for tofacitinib 5 mg BID and adalimumab (consistent with previous studies, which report higher absolute SIE risk in older patients but similar relative risk with TNFi in older vs younger patients),[6 7] while the risk was significantly greater in older versus younger patients with tofacitinib 10 mg BID.

In the registry data set (total, n=10 357; tofacitinib, n=1999; biologic disease-modifying antirheumatic drug (bDMARD), n=8358), age-/gender-standardised SIE IRs were higher in older versus younger patients, and similar between tofacitinib and bDMARD initiators for both age groups (online supplemental figure S2).

Our results are consistent with a real-world analysis of >130 000 RA patients, which reported similar adjusted SIE HRs for tofacitinib versus six of seven bDMARDs, including adalimumab.[8] Limitations of the present analyses should be considered. The clinical data set included variations in sample size and patient-years of exposure between treatment and

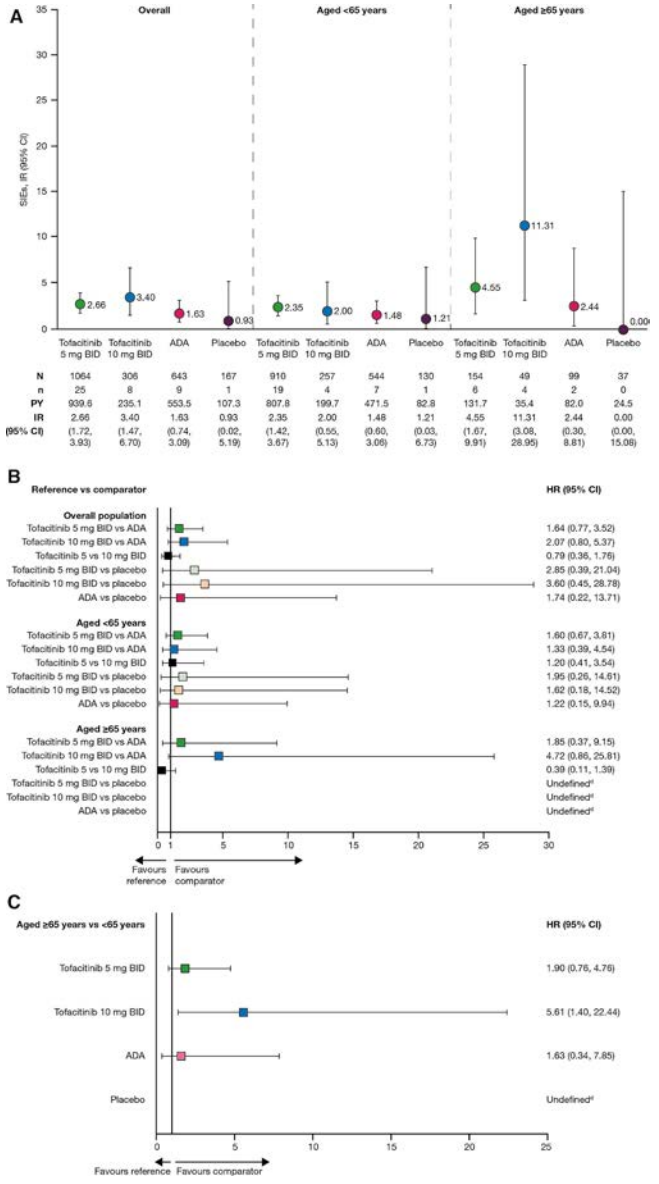

Figure 1 (A) IRs (95% CI) and (B) HRs[a] (95% CI) between treatment groups, overall and stratified by age (<65 years or ≥65 years) and (C) HRs[b] (95% CI) between age groups for each treatment group, for SIEs in pooled Phase 2, 3 and 3b/4 studies (months 0 to 12).
[c] Pooled data from Phase 2 (A3921035; NCT00550446), Phase 3 (ORAL Standard; NCT00853385) and Phase 3b/4 (ORAL Strategy; NCT02187055) studies. IR=unique patients with events/100 PY. [a]Cox proportional hazards model includes treatment as the only factor. [b]Cox proportional hazards model includes treatment, age group (<65 years or ≥ 65 years) and treatment by age group interaction terms. [c]For Study A3921035, only data within the first 3-month randomised parallel treatment period were included (before patients who were receiving ADA were switched to tofacitinib 5 mg BID after month 3). [d]Could not be defined as there were 0 events in the placebo group. ADA, adalimumab; BID, twice daily; IR, incidence rate; N, number of treated patients; n, number of patients with event; PY, patient-years; SIE, serious infection event.

age groups, and low numbers of older patients and events in some treatment groups which led to wide 95% CIs or undefined relative risk estimates. Additionally, registry data were not matched for baseline variables beyond age/gender.

In conclusion, as would be expected, SIE incidence was higher in older versus younger patients. SIE risk was similar between age groups with tofacitinib 5 mg BID and adalimumab but higher in older versus younger patients with tofacitinib 10 mg BID, suggesting an effect modification by age for this dose. Real-world data showed similar SIE risk for patients initiating tofacitinib or bDMARDs despite limited baseline matching. These data support the globally recommended dose of 5 mg BID for RA.

Kevin L Winthrop ,[1] **Gustavo Citera,**[2] **David Gold,**[3] **Dan Henrohn,**[4] **Carol A Connell,**[5] **Andrea B Shapiro,**[6] **Harry Shi,**[7] **Alina M Onofrei,**[8] **Dimitrios A Pappas** ,[9] **Hendrik Schulze-Koops** [10]

[1]Division of Infectious Diseases, Oregon Health & Science University, Portland, Oregon, USA
[2]Section of Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina
[3]Pfizer Inc, Montreal, Quebec, Canada
[4]Pfizer Inc, Sollentuna, Sweden
[5]Pfizer Inc, Groton, Connecticut, USA
[6]Pfizer Inc, Peapack, New Jersey, USA
[7]Pfizer Inc, Collegeville, Pennsylvania, USA
[8]Corrona LLC, Waltham, Massachusetts, USA
[9]Department of Medicine, Columbia University, New York, New York, USA
[10]Division of Rheumatology and Clinical Immunology, Department of Internal Medicine IV, University of Munich, Munich, Bayern, Germany

Correspondence to Dr David Gold, Pfizer Inc, Montreal, QC H9J 2M5, Canada; David.Gold@pfizer.com

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Data availability statement Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or European Union, or (2) in programmes that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer. The Corrona data set is based on a large US multicentre study adhering to a number of institutional review boards, with complex logistics. Patients did not provide consent to raw data sharing during the data collection for this purpose, and the Corrona data sharing policies do not permit raw data sharing for this purpose. An aggregated limited data set from the current analyses is available to qualified investigators with an approved protocol. Data requests may be sent to Corrona, represented by Dr Jeffrey D Greenberg, MD, MPH, Corrona LLC, Waltham, Massachusetts, and NYU School of Medicine, New York, New York, USA. E-mail jgreenberg@corrona.org.

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ORCID iDs
Kevin L Winthrop http://orcid.org/0000-0002-3892-6947
Dimitrios A Pappas http://orcid.org/0000-0001-8338-027X
Hendrik Schulze-Koops http://orcid.org/0000-0002-1681-491X

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Management of rheumatic diseases in the time of covid-19 pandemic: perspectives of rheumatology practitioners from India

With respect to observations by Monti *et al*,[1] a survey featuring 31 questions related to rheumatic diseases (RDs) during the covid-19 pandemic was administered to members of the Indian Rheumatology Association.

Of 861 invitees, 221 (25.7%; 92.7% adult rheumatologists, 52.2% academicians) responded. Most perceived the need for a change in the management of RDs (online supplementary files). Almost half (47.5%) reduced the usage of biological disease modifyinig anti rheumatic drugs (bDMARDs), whereas only 12.2% did so for csDMARDs (figure 1). Of the respondents, 66.5% were more inclined to initiate hydroxychloroquine (HCQ) in patients with borderline indications, whereas 14% disagreed with this approach. Nearly two-thirds (64.2%) were less inclined to change the major immunosuppressant (IS) for impending flare, with 58.3% deferring rituximab (RTX), followed closely by cyclophosphamide, antitumour necrosis factors (anti-TNFs), Janus kinase inhibitors (JAKinibs) and other bDMARDs. An earlier taper of glucocorticoids was preferred by 57.9% in inactive disease. There was lack of consensus on continuing IS infusions.

HCQ was preferred for treatment of covid-19 (81.9%), followed by protease inhibitors (22.17%) and intravenous immunoglobulin (IVIG) (8.14%). Chloroquine was less popular (19%). Almost three-fourths (70.5%) felt that covid-19 could cause macrophage activation syndrome (MAS) and preferred tocilizumab for its treatment (27.6%). Of the respondents, 22.6% advocated (and prescribed) HCQ prophylaxis, while 27.2% were unsure and 50.2% disagreed.

The most prevalent fears were transmitting covid-19 to family members, followed by patients getting infected and the physicians themselves getting infected.

Greater risk of viral activation has been described with RTX and JAKinibs, and thus reluctance in usage of bDMARDs and tsDMARDs is not unfounded. However, data are scarce on the specific risk of respiratory viral infections due to JAKinibs. While some have advocated the use of JAKinibs to inhibit cellular entry of covid-19, this might be successful at supratherapeutic doses, raising significant safety concerns.[2] However, data on risk of influenza with anti-TNFs are lacking. IVIG usage was favoured by a minority; however, it still merits consideration. Patients with RDs could possibly have a heightened risk, as sizeable numbers are elderly or have comorbid cardiac or lung disease.

Disease flares can potentially be induced by covid-19, as seen in RDs by most endogenous retroviruses as well as acquired viral infections.[3] While most rheumatologists believed that covid-19 may trigger MAS, it might be difficult to distinguish cytopaenia and hyperferritinaemia due to increased disease activity. The consensus was on the use of tocilizumab in MAS, backed by a case series which remains to be confirmed in ongoing trials.[4] The feasibility of screening for severe acute respiratory syndrome

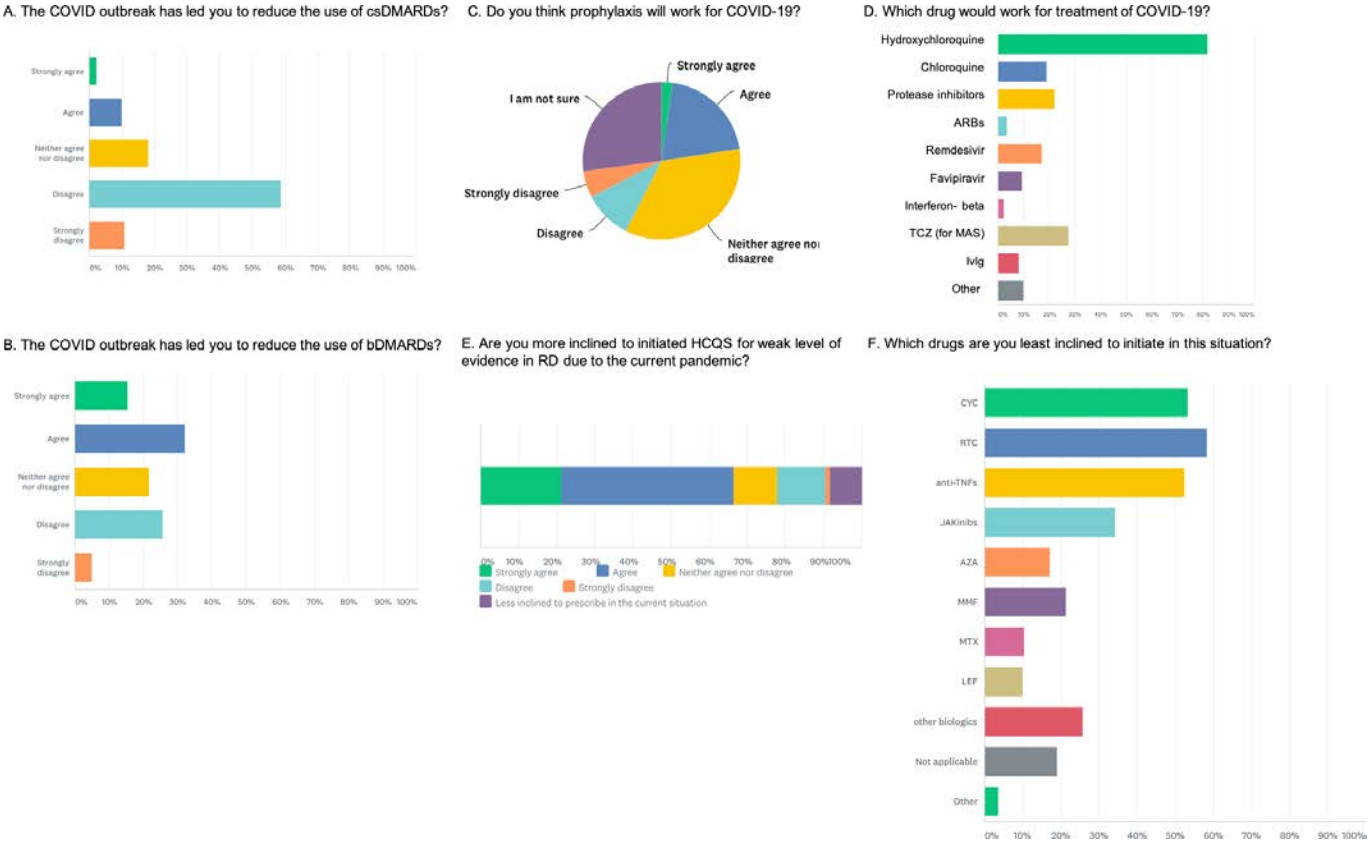

Figure 1 Opinion of rheumatologists on change in management of rheumatic diseases in the time of covid-19 pandemic. ARBs, angiotensin receptor blockers; AZA, Azathioprine; bDMARDs, biological disease modifying anti rheumatic drugs; csDMARDs, conventional synthetic disease modifying anti rheumatic drugs; CYC, cyclophosphamide; HCQ, hydroxychloroquine; IVIG, intravenous immunoglobulin; JAKinibs, Janus kinase inhibitors; LEF, Leflunomide; MAS, macrophage activation syndrome; MMF, Mycophenolate mofetil; MTX, Methotrexate; RD, rheumatic disease; RTX, Rituximab; TCZ, Tocilizumab; TNF, tumour necrosis factor.

Coronavirus-2 before initiation of bDMARDs needs to be explored as previously suggested.[5]

There was unanimous agreement on use of HCQ for treatment of covid-19, even in patients with otherwise low evidence base. This may be attributed to its safety profile, greater in vitro efficacy against covid-19 and greater experience with HCQ as rheumatologists. However, caution is needed as reports of toxicity have emerged with the use of prophylaxis.

The management of the connective tissue disorders spectrum of RDs is more likely to be changed, suggesting the need to develop evidence for a triage-in-rheumatology protocol bracing for the times ahead.

A strength of our survey was that 60% of the respondents had been in rheumatology practice for more than 5 years. Mhaskar *et al*[6] have reported 73% concordance between decision analysis driven by expert consensus and evidence gathered from randomised controlled trials. Considering the potential limitations of generating evidence in the face of a global crisis, it might be imperative to embark on a Delphi exercise to generate expert opinion, while data from covid-19 rheumatology registries in progress are awaited.

The present survey provides the viewpoint of a large number of rheumatologists and could shape future evidence-based opinions on managing patients with IS during the covid-19 pandemic.

Latika Gupta ,[1] **Durga Prasanna Misra** ,[1] **Vishwesh Agarwal**,[2] **Suma Balan**,[3] **Vikas Agarwal**[1]

[1]Clinical Immunology and Rheumatology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, UP, India
[2]Mahatma Gandhi Mission's Medical College, Navi Mumbai, Maharashtra, India
[3]Department of Paediatric Rheumatology, Amrita Institute of Medical Sciences and Research Centre, Cochin, Kerala, India

Correspondence to Dr Vikas Agarwal, Department of Clinical Immunology and Rheumatology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow 226014, India; vikasagr@yahoo.com

Correction notice This article has been corrected since it published Online First. Figure 1 has been replaced.

Twitter Latika Gupta @LatikaGupta_

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ORCID iDs
Latika Gupta http://orcid.org/0000-0003-2753-2990
Durga Prasanna Misra http://orcid.org/0000-0002-5035-7396

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Antirheumatic agents in covid-19: is IL-6 the right target?

The letter of Monti *et al*[1] on covid-19 in patients with chronic arthritis treated with immunosuppressive therapies stimulates some considerations.

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infects cells through the ACE-2 receptor, which is highly expressed in both the lung and the heart. Besides direct tissue injury, SARS-CoV-2 infection can also induce an exaggerated host immune response, frequently inducing a cytokine release syndrome contributing to multiorgan dysfunction. Indeed, high levels of circulating cytokines, particularly interleukin (IL)-6, IL-1β and tumour necrosis factor-alpha (TNFα), are commonly found in patients with covid-19, correlating with mortality (IL-6).[2]

Current therapeutic strategy involves agents counteracting viral invasion and replication, and inhibitors of cytokine-sustained inflammatory reactions. Indeed, different cytokines involved in the acute inflammatory response are currently targeted by specific medications otherwise employed in the treatment of rheumatic diseases. Agents inhibiting the activity of IL-1β, TNFα, IL-6 and the Janus Kinase 1 and 2 (JAK 1/2)-Signal Transducer and Activator of Transcription (STAT) pathway are currently under consideration in the treatment of covid-19-associated respiratory syndrome.[3]

We are here providing some arguments to help achieve a more rational therapeutic decision. In any case, as a general consideration, the short-term period of administration of these agents is unlikely to produce a significant immunosuppressive activity.

Acute inflammatory response to infective agents is mainly driven by innate immunity, with a rapid (30 min) increase in TNFα and IL-1β levels synergistically contributing to a subsequent rise of IL-6, which in turn inhibits TNFα and IL-1β release. Higher IL-6 levels are longer lasting, while TNFα and IL-1β levels rapidly (24–48 hours) decrease.[4] Thus, the therapeutic window for anti-TNFα and anti-IL-1β agents is very narrow. As a consequence, before the administration of agents targeting specific cytokines, serum levels of these cytokines should be obtained. Further considerations arise from data from chest X-ray or CT. Consolidation pattern, often present in covid-19, recalls organising pneumonia,[5] which is associated with a cytokine profile characterised by a major involvement of IL-6, rather than TNFα and IL-1β. Accordingly, the IL-6 receptor antagonist tocilizumab was effective in the treatment of refractory organising pneumonia associated with Sjögren's disease.

Cardiovascular manifestations are also common in covid-19 infection, with a percentage of arrhythmias up to 16.7% and with 5.9% of malignant ventricular tachyarrhythmias also associated with QTc interval prolongation induced by medications and electrolyte derangement. In this regard, systemic inflammation via elevated IL-6, but not TNFα and IL-1β serum levels, has been shown to represent a novel QT-prolonging risk factor contributing to torsade de pointes occurrence in the presence of other risk factors.[6]

Accordingly, it seems of relevance to stress that in rheumatoid arthritis, where the arrhythmic risk is increased often leading to sudden cardiac death and levels of circulating inflammatory cytokines correlate with QTc duration, IL-6 receptor blockade by tocilizumab promptly induced a significant QTc shortening correlating with the decrease in C reactive protein and cytokine levels.[6] Moreover, a single administration of the drug in subjects with non-ST-elevation myocardial infarction reduced inflammatory response and myocardial injury, with no safety issues (including infections) in the following 6 months.

In light of these considerations, pharmacological interference on the IL-6 system, either by blocking the IL-6 receptor (tocilizumab, sarilumab) or inhibiting the JAK 1/2-STAT pathway (baricitinib, ruxolitinib), should find a more rational indication in dampening the systemic inflammatory response in covid-19, not only to control lung involvement, but also to reduce acute cardiovascular complications, including QT-related arrhythmic events.

Pier Leopoldo Capecchi ,[1] **Pietro Enea Lazzerini,**[1] **Luca Volterrani,**[2] **Maria Antonietta Mazzei,**[2] **Barbara Rossetti,**[3] **Giacomo Zanelli,**[4] **David Bennett,**[5] **Elena Bargagli,**[6] **Federico Franchi,**[7] **Matteo Cameli,**[8] **Serafina Valente,**[9] **Luca Cantarini,**[10] **Bruno Frediani**[10]

[1]Department of Medical Sciences, Surgery and Neurosciences, Section of Internal Medicine, COVID-19 Unit, Siena University Hospital, Siena, Toscana, Italy
[2]Department of Medical Sciences, Surgery and Neurosciences, Section of Radiology, COVID-19 Unit, Siena University Hospital, Siena, Toscana, Italy
[3]Section of Infectious Diseases, COVID-19 Unit, Siena University Hospital, Siena, Toscana, Italy
[4]Department of Medical Biotechnologies, Section of Infectious Diseases, COVID-19 Unit, Siena University Hospital, Siena, Toscana, Italy
[5]Section of Pneumology, COVID-19 Unit, Siena University Hospital, Siena, Toscana, Italy
[6]Department of Medical Sciences, Surgery and Neurosciences, Section of Pneumology, COVID-19 Unit, Siena University Hospital, Siena, Toscana, Italy
[7]Department of Medical Sciences, Surgery and Neurosciences, Section of Intensive Care, COVID-19 Unit, Siena University Hospital, Siena, Toscana, Italy
[8]Department of Medical Biotechnologies, Section of Cardiology, COVID-19 Unit, Siena University Hospital, Siena, Toscana, Italy
[9]Section of Cardiology, COVID-19 Unit, Siena University Hospital, Siena, Toscana, Italy
[10]Department of Medical Sciences, Surgery and Neurosciences, Section of Rheumatology, COVID-19 Unit, Siena University Hospital, Siena, Toscana, Italy

Correspondence to Professor Pier Leopoldo Capecchi, Department of Medical Sciences Surgery and Neurosciences, Section of Internal Medicine, COVID-19 Unit, Siena University Hospital, Siena 53100, Italy; capecchipl@unisi.it

Contributors PLC: conception and design of the work, acquisition, analysis or interpretation of data, drafting the work, final approval of the version published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. PEL: substantial contribution to the conception or design of the work and revising the manuscript critically for important intellectual content, final approval of the version published. LV, MAM: substantial contribution to the part of the work involving X-ray and revising the manuscript critically for important intellectual content, final approval of the version published. BR, GZ: substantial contribution to the part of the work involving virus infection and revising the manuscript critically for important intellectual content, final approval of the version published. DB, EB: substantial contribution to the part of the work involving lung injury and revising the manuscript critically for important intellectual content, final approval of the version published. FF: substantial contribution to the part of the work involving intensive care and revising the manuscript critically for important intellectual content, final approval of the version published. MC, SV: substantial contribution to the part of the work involving heart damage and revising the manuscript critically for important intellectual content, final approval of the version published. LC: substantial contribution to the part of the work involving antirheumatic agents and revising the manuscript critically for important intellectual content, final approval of the version published. BF: substantial contribution to the conception of the work and to the part of the work involving antirheumatic agents and revising the manuscript critically for important intellectual content, final approval of the version published. The authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ORCID iD
Pier Leopoldo Capecchi http://orcid.org/0000-0001-7021-7764

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The conundrum of COVID-19 treatment targets: the close correlation with rheumatology. Response to: 'Management of rheumatic diseases in the time of covid-19 pandemic: perspectives of rheumatology pracitioners from India' by Gupta *et al* and 'Antirheumatic agents in covid-19: is IL-6 the right target?' by Capeechi *et al*

We thank Capecchi *et al*[1] for their comment on our paper. The authors suggested that interleukin 6 (IL-6) represents the key cytokine responsible for the majority of pulmonary and cardiovascular complications of COVID-19. Similarly, we have received a comment from Gupta *et al*[2] who reported the management of rheumatological treatments during COVID-19 pandemic among practitioners in India, revealing that choices were apparently made according to the beliefs on the possible relationships between drug mechanism of action and effect on the viral infection. Both correspondence comments highlighted some striking similarities with changes seen in rheumatological conditions such as the systemic effects of chronic inflammation in rheumatoid arthritis, or laboratory findings resembling macrophage activation syndrome, and argued on the potential applications of rheumatological targeted therapies in this new context, especially on the central role of IL-6 inhibitors. Gupta *et al* also reported that approximately half of the practitioners would reduce the use of biological disease modifying antirheumatic drugs or defer specific drugs such as rituximab or cyclophosphamide.[2] As reported in our previous paper,[3] although caution is warranted, we believe that preventive insufficient treatment of rheumatological conditions would expose patients to the risk of severe morbidity and mortality connected to the underlying disease. Moreover, uncontrolled disease activity would further increase the risk of infection in these patients, and expose them to an additional burden of inflammation with the possible consequences described by Capecchi *et al*,[1] and possible confounding of the clinical picture with challenging management issues. Nevertheless, we acknowledge that more evidence is needed to guide decisions in the treatment of susceptible immunocompromised patients during the ongoing COVID-19 outbreak. Indeed, the molecular and immunological response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has not yet been fully elucidated. It is hypothesised that the disease is characterised by different stages.[4] An initial viral phase which would possibly benefit from direct antiviral agents, but also from immunoadjuvant drugs such as type 1 interferon,[5] could then shift towards a gradual, individual-based, host-dependent excessive inflammatory response, probably more susceptible to immunosuppressive treatments, such as IL-6 inhibitors or other targeted drugs.[6] Nevertheless, this is most certainly an oversimplification of the immunopathological changes occurring during SARS-CoV-2 infection, and it is unlikely that the complexity of acute inflammation which progresses through the cellular crosstalk, immune system activation, metabolic changes and coagulation activation may be fully tackled by blocking a singular cytokine target. Moreover, identifying the correct timing to shift the treatment strategy according to the different biological stages of a scarcely known viral disease is particularly challenging. Preliminary, uncontrolled clinical studies have supported a role of IL-6 inhibition in some patients with severe COVID-19.[7 8] Nonetheless, definitive evidence should be awaited from the ongoing randomised controlled trials being conducted on this and other rheumatological targeted drugs. As further high-quality evidence on the nature of SARS-CoV-2 and its immunomodulatory treatment accumulates, there will also be more information to support rheumatologists in the management of their patients receiving chronic treatments, often including the same agents now being tested for COVID-19.

Sara Monti , **Carlomaurizio Montecucco**

Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Correspondence to Dr Sara Monti, Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia 27100, Italy; sara.saramonti@gmail.com

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ORCID iD
Sara Monti http://orcid.org/0000-0002-1800-6772

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Online management of rheumatoid arthritis during COVID-19 pandemic

We have read with great interest the recent article from Figueroa-Parra *et al*[1] entitled 'Are my patients with rheumatic diseases at higher risk of COVID-19?' We agree that patients with rheumatic diseases are at higher risk of communicable diseases such as COVID-19, and protective measures are required.

Patients with rheumatic diseases need frequent doctor appointments to get tailored and individualised therapies.[2] However, during the COVID-19 pandemic, most outpatient services were cancelled to avoid cross-infection. Besides, visiting hospitals puts these patients at higher risk of being infected, in consideration of their advanced age and comorbidities.[3] Thus one of the critical elements is the management of these chronic diseases, such as rheumatoid arthritis (RA), in a non-face-to-face method.

We had performed online healthcare services on different platforms, including but not limited to web-based hospital, WeChat, HaoDaiFu Online and TikTok. From 25 January to 31 March, 76 patients with RA were involved in online management, aiming for medications (47.4%), health condition evaluation (39.5%) and psychological guidance (13.1%). A series of popular medical articles had been uploaded which could help in improving patients' understanding of their health conditions. Patients were provided with questionnaires for disease severity and function status, and prescription medications could be delivered by express service according to patients' demand. They were pleased with their experience of our online management, where we got an average score of 4.6 out of 5 in patient satisfaction assessment. Interestingly, it was found that during the epidemic outbreak, there was a good opportunity to perform popular medical science, probably because more attention was paid to personal health conditions.

Based on our experience, patients are able to get access to medical services and medications without hospital appointments via online tools. For social healthcare system, online medical services deploy a large number of doctors in a short time, avoid overwhelmed outpatient service and reduce cross-infection by avoiding face-to-face interviews.[4] These telehealth services would be effective tools for both doctors and patients, especially during public health emergencies.

Yang Zhang, Jian Wang, Liang Zhao, Jun Xiao, Zhanjun Shi

Division of Orthopaedic Surgery, Department of Orthopaedics, Nanfang Hospital, Southern Medical University, Guangzhou, China

Correspondence to Dr Zhanjun Shi, Department of Orthopaedics, Southern Medical University Nanfang Hospital, Guangzhou 510515, China; nfgk@sohu.com

Contributors YZ and ZS designed the study and wrote the letter. YZ and ZS analysed the data. YZ, JW, LZ and JX performed the online medical service.

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ORCID iD
Zhanjun Shi http://orcid.org/0000-0003-4772-4367

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Challenges and opportunities in telerheumatology in the COVID-19 era. Response to: 'Online management of rheumatoid arthritis during COVID-19 pandemic' by Zhang *et al*

We thank Zhang *et al* for the interest showed in our letter[1] and appreciate their comments about the care of rheumatic patients during the COVID-19 pandemic.[2] We agree that the function of all rheumatology outpatient clinics around the world has changed. It is a fact that the complexity of the care of rheumatic disease patients implies challenges, both to follow-up knew patients and control their diseases and also in the evaluation of patients with onset of new symptoms who potentially could be caused by a rheumatic disease. In patients with rheumatoid arthritis (RA), from the five clinical encounter components (vital signs, patient history, physical examination, laboratory tests and ancillary studies), patient's history and physical examination are the most important in their diagnosis and management compared with other diseases.[3]

Telemedicine is not a new idea; it has been used in many countries for years to improve access to specialised care in rural areas. In telemedicine, we can obtain a complete patient's history, but we have some barriers to the physical examination. Even when we can do a proper inspection of skin lesions or identify swollen joints, it is more difficult to evaluate lung abnormalities or perform certain types of manoeuvres to identify the origin of pain. Telemedicine and telehealth approaches have taken a predominant role in our practices in the past months. It has been proposed a triage tool to guide telemedicine in rheumatology that depends on the diagnosis stage and disease state; according to this tool, good candidates to telemedicine could be those with established diagnosis and stable disease and those who need a screening prior to the in-person visit, but may not be the best option to those patients who are having a flare, need a procedure or the complexity of their disease and follow-up is difficult to do remotely.[4] We proposed as an alternative to use during telemedicine consultation for patients with RA, the combination of routine assessment of patient index data 3 (RAPID3) score[5] and the evaluation of fist closure and fist strength[6] both of them have shown good correlation with other activity scales (that includes joint-counts) and underlying flexor tenosynovitis, respectively. The lack of telecommunication resources in low-income and middle-income countries makes the possibility of offering this type of care more difficult than others. Nonetheless, the benefits are more numerous (convenience, decreased costs of transportation to hospitals or clinics, accessibility for patients leaving in other states or countries), and particularly aim to protect patients, doctors and staff from unnecessary risk of contracting COVID-19. Work has to be done to implement these means as an aid measure in cases where medical consultation is compromised.

We believe that all the changes that we are living in also carry opportunities to innovate and optimise the care access to our patients. There will be changes that will stay from now on and we are obligated to learn, adapt and evolve by optimising these resources in performing a better healthcare approach for our patients.

Gabriel Figueroa-Parra , Carmen Magdalena Gamboa-Alonso, Dionicio Angel Galarza-Delgado

Servicio de Reumatología, Hospital Universitario Dr José Eleuterio González, Monterrey, Nuevo León, Mexico

Correspondence to Dionicio Angel Galarza-Delgado, Servicio de Reumatología, Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Nuevo León, Mexico; dgalarza@medicinauanl.mx

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Twitter Gabriel Figueroa-Parra @GaboFP

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ORCID iDs
Gabriel Figueroa-Parra http://orcid.org/0000-0002-6077-8899
Dionicio Angel Galarza-Delgado http://orcid.org/0000-0001-9714-2109

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Hydroxychloroquine reduces the risk of covid-19 in patients with rheumatic diseases: myth or reality?

We read with great interest the article by Figueroa-Parra *et al* illustrating whether patients with rheumatic diseases are at higher risk of the coronavirus disease 2019 (covid-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] In this study, the authors mentioned the potential benefit of antimalarial drugs for patients with rheumatic diseases in the context of covid-19 pandemic. At present, that is the really pivotal question, whether the antimalarial drugs could reduce the risk of SARS-CoV-2 infection in patients with rheumatic diseases.

Hydroxychloroquine (HCQ) and chloroquine, as antimalarial drugs for more than 70 years, have been successfully used to treat variety of rheumatic diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. Both drugs have a flat aromatic core structure and share nearly identical mechanism of action, but HCQ has replaced chloroquine in most countries due to its much better safety profiles. In vitro and in vivo assays, chloroquine treatment was found to be effective against coronavirus infections, including SARS-CoV-2 and has been recommended as an antiviral therapy in the latest Chinese guideline for the management of covid-19.[2] Regarding the HCQ, Yao *et al* first confirmed HCQ was found to be more potent than chloroquine in SARS-CoV-2 inhibition in vitro.[3] In humans, an open-label non-randomised clinical trial reported HCQ treatment (600 mg/day for 10 days) is efficient for virus elimination and its effect is reinforced by azithromycin.[4] Meanwhile, a randomised clinical trial (ChiCTR2000029559) of 62 covid-19 patients also suggested the use of HCQ (400 mg/day for 5 days) could significantly shorten time to clinical recovery and promote the absorption of pneumonia. On the contrary, a prospective study of 11 patients (600 mg/day for 10 days) and a pilot study of 30 patients (400 mg/day for 5 days) failed to replicate the significant efficacy of HCQ.[5 6] For patients with rheumatic diseases, previous clinical researches showed median blood HCQ concentration in patients with cutaneous lupus erythematosus and SLE who received HCQ 400 mg daily is 758 (2.26) and 917 (2.73) ng/mL (μM), respectively.[7 8] In vitro, HCQ was found to decrease the viral replication in a concentration-dependent manner, with EC50 values of 6.25 and 6.14 µM at 24 hours before or after SARS-CoV-2 exposure, respectively.[3] However, HCQ has a wide distribution in lung where HCQ concentration reaches hundred times more than that in the blood, and this unique property might lead to enough high concentration necessary for inhibitory effects on the lung compartments.[3] Although lung is the major organ to be injured during SARS-CoV-2 infection, it should be noted that SARS-CoV-2 receptor is widely expressed in various organs or tissues (heart, kidney and bile ducts) and definite effect of HCQ on SARS-CoV-2 infection among patients with rheumatic diseases and treated with HCQ 400 mg daily is not unequivocal.

Notably, despite the proven favourable safety, HCQ may cause several serious adverse events in patients with rheumatic diseases at a higher daily or cumulative dose, such as retinopathy and cardiotoxicity, especially in those with primary heart disease or liver dysfunction.[9] Therefore, rheumatologists are advised to fully consider the risks and benefits before initiating the HCQ therapy or increasing HCQ daily dose and patients with rheumatic diseases should not take, stop or change the dose of HCQ without healthcare provider's permission.

Wenhui Xie , **Yu Wang, Zhuoli Zhang**

Department of Rheumatology and Clinical Immunology, Peking University First Hospital, Beijing, China

Correspondence to Professor Zhuoli Zhang, Department of Rheumatology and Clinical Immunology, Peking University First Hospital, Beijing, China; zhuoli.zhang@126.com

Contributors WX and YW wrote the paper. ZZ reviewed and edited the manuscript. All authors have read and approved the content of the manuscript.

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ORCID iDs
Wenhui Xie http://orcid.org/0000-0002-3881-0266
Zhuoli Zhang http://orcid.org/0000-0001-7219-9141

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Still early to define a clear role of antimalarial drugs for COVID-19 in patients with rheumatic disease. Response to: 'Hydroxychloroquine reduces the risk of covid-19 in patients with rheumatic diseases: myth or reality?' by Xie *et al*

We thank Xie *et al*[1] for the interest in our letter[2] and found some relevant points to discuss the role of antimalarial drugs during the COVID-19 pandemic. The information has increased at an incredible rate since our letter was published. Despite initial encouraging in vitro and preclinical studies, current evidence supporting the role of antimalarial drugs for prophylaxis or treatment of COVID-19 has been predominantly contradictory or negative.[3]

COVID-19 was classified as a pandemic on 11 March 2020 by WHO.[4] To this date (7 June 2020), 6 799 713 cases have been confirmed worldwide, with 397 388 deaths.[5]

The severity and mortality of this virus have motivated researchers to find an effective treatment. Many prophylaxis (pre-exposure and postexposure) trials are currently running. Boulware *et al* conducted a randomised, double-blind trial in the USA and Canada that tested postexposure prophylaxis with hydroxychloroquine (HCQ) or placebo. They included 821 asymptomatic participants with moderate or high-risk exposure to receive within 4 days of the exposure HCQ or placebo, no significant difference in the rate of confirmed or probable COVID-19 were found between groups, side effects were more frequent in the HCQ than in the placebo group, but no serious adverse events were reported.[6] Some limitations of the report included the low number of PCR-confirmed cases, the recruitment methodology, the participant-reported data and the variable time to start HCQ.[7]

A systematic review of antimalarial drugs in COVID-19 concluded that current evidence is weak, insufficient and conflicting. The review included 4 randomised controlled trials, 10 cohort studies and 9 case series. Adverse events information from the studies included was also limited to draw solid conclusions and evaluate the risk–benefit of these interventions.[3]

In an observational study of hospitalised patients with COVID-19, HCQ administration was not associated with decreased intubation or death.[8] Recently, a study that demonstrated an inefficient response with the use of antimalarial drugs to treat COVID-19 and showed an increased risk of de novo ventricular arrhythmias retracted from these findings, only demonstrating the need to continue research on the subject and the risk of taking therapeutic decisions with these early results.[9]

The COVID-19 Global Rheumatology Alliance system has reported 2102 provider registration cases and 12 499 patient's survey registration cases of COVID-19 in rheumatic patients.[10] The first report including 600 patients with rheumatic disease with confirmed COVID-19 from 40 countries showed that 46% were hospitalised and 9% died. The most common diagnoses were rheumatoid arthritis (38%) and systemic lupus erythematosus (SLE) (14%). Patients with SLE (OR 1.8), vasculitis (OR 1.56) and axial spondyloarthritis (OR 1.11) were at increased risk of hospitalisation. Higher rates of hospitalisation were associated with older age and comorbidities (hypertension, lung disease, diabetes, cardiovascular disease and chronic kidney disease). The use of prednisone (>10 mg/day) was also associated with an increased risk of hospitalisation. Anti-TNF use was associated with decreased hospitalisation rates (OR 0.4) independently on antimalarial drug use (OR 0.94).[11 12]

The EULAR and ACR groups have suggested several recommendations in the use of antimalarial drugs, stating to continue this treatment if this were given previously, not augmenting the dose as prophylaxis or treatment of COVID-19, and not implementing the use of these drugs for this reason.[13 14]

With all this previously portrayed, we continue to think that it is still early to define a clear role of antimalarial drugs for COVID-19 treatment in patients with rheumatic disease and consider more studies should be performed before recommending the implementation of these drugs in our clinical practice as prophylaxis or treatment. Hopefully, as clinical evidence accumulates, the real risk our rheumatic patients have will become clearer.

Carmen Magdalena Gamboa-Alonso, Gabriel Figueroa-Parra, Dionicio Angel Galarza-Delgado

Servicio de Reumatología, Hospital Universitario Dr José Eleuterio González, Monterrey, Nuevo León, Mexico

Correspondence to Dionicio Angel Galarza-Delgado, Servicio de Reumatología, Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey 64460, Mexico; dgalarza@medicinauanl.mx

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ORCID iDs
Gabriel Figueroa-Parra http://orcid.org/0000-0002-6077-8899
Dionicio Angel Galarza-Delgado http://orcid.org/0000-0001-9714-2109

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To consider or not antimalarials as a prophylactic intervention in the SARS-CoV-2 (COVID-19) pandemic

I read with great interest the letter by Spinelli *et al* published in the *Annals of the Rheumatic Diseases*.[1] The authors describe the existing scientific evidence concerning the potential antiviral activity of chloroquine and hydroxychloroquine (HCQ) against SARS-CoV-2 (COVID-19) infection in vitro, and the available clinical studies.

In my opinion, caution must be exercised before drawing any conclusions about the efficacy of antimalarials as prophylactic or therapeutic options for COVID-19 infection, given the concerns raised by healthcare providers related to inadequate supply for patients with chronic conditions such as systemic lupus erythematosus and rheumatoid arthritis.[2]

So far, there is no substantial evidence to support the beneficial role of antimalarials. In particular, the authors cited an article by Gao *et al*,[3] which reported that the administration of chloroquine phosphate in 100 Chinese patients with COVID-19 infection was superior, compared with the control group, on the following endpoints: exacerbation of pneumonia, improvement of radiographic findings, virus-negative conversion and disease duration. Surprisingly, the authors did not provide any information about demographics, if the patients were hospitalised or not, the clinical characteristics of both groups, baseline treatment regimens, and the primary or secondary endpoints.

In contrast to the above report, a small pilot study from China showed no difference between HCQ-treated patients compared with a control group in terms of negative conversion rate of pharyngeal swabs, duration of fever and radiographic progression on CT chest images.[4]

Anecdotal reports from registries of patients with COVID-19 infection and autoimmune rheumatic diseases demonstrated that approximately 25% of infected patients were already taking HCQ, indicating HCQ might not have any protective effect.

Lastly, we agree with the authors of the urgent need for large clinical trials to assess the efficacy and safety of antimalarial treatments in patients with COVID-19 infection.

Konstantinos Parperis [1,2]

[1]Internal Medicine, Division of Rheumatology, University of Cyprus Medical School, Nicosia, Cyprus
[2]Medicine, Division of Rheumatology, University of Arizona College of Medicine, Phoenix, Arizona, USA

Correspondence to Dr Konstantinos Parperis, Internal Medicine, Division of Rheumatology, University of Cyprus Medical School, Nicosia 1678, Cyprus; kparpe02@ucy.ac.cy

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ORCID iD
Konstantinos Parperis http://orcid.org/0000-0001-6009-0130

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Response to 'To consider or not antimalarials as a prophylactic intervention in the SARS-CoV-2 (Covid-19) pandemic' by Parperis

We thank Konstantinos Parperis for his correspondence to our letter 'To consider or not antimalarials as a prophylactic intervention in the SARS-CoV-2 (Covid-19) pandemic' speculating on prophylactic use of antimalarials for subjects at high risk of getting infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1 2]

As the author highlights, at this time, it is preferable to be cautious when addressing this topic. These days, the scientific information is moving faster than usual, and new data are available every day; however, the scientific evidence collected to date is not robust enough and not unequivocal. The pathogenesis of Covid-19 is still largely unknown and the precise effect of antimalarial drugs in Covid-19 patients is not fully predictable. Every day new data are accessible, even though not conclusive and not yet supporting a role for antimalarials in the management of SARS-Cov-2 infection, especially in critically ill patients.[3] The enthusiastic reactions for the early French study by Gautret *et al*, showing a fast virus clearance in patients with Covid-19 treated with hydroxychloroquine, have not found confirmation in all the subsequent observations.[4–8] In any case, the empiric use of hydroxychloroquine has already been diffused in many countries.[9]

The issue of fair allocation of resources during the Covid-19 pandemic is a matter of debate. Even appreciating the great efforts to manage the current pandemic in the best possible way, as rheumatologists, we should feel obliged to consider the care of our patients with autoimmune rheumatic diseases, in which hydroxychloroquine and chloroquine have demonstrated their efficacy. As we stated at the end of the letter, a major concern is the possible effect of a wide use of antimalarials on their global supply. For sure, treatment of Covid-19 with hydroxychloroquine and chloroquine should not compromise the chronic therapy of patients with rheumatological diseases.

Francesca Romana Spinelli , Fulvia Ceccarelli , Manuela Di Franco, Fabrizio Conti

Dipartimento di Scienze Cliniche, Internistiche, Anestesiologiche e Cardiovascolari—Reumatologia, Sapienza University of Rome, Roma, Italy

Correspondence to Dr Francesca Romana Spinelli, Dipartimento di Scienze Cliniche, Internistiche, Anestesiologiche e Cardiovascolari - Reumatologia, Sapienza University of Rome, Roma 00161, Italy; francescaromana.spinelli@uniroma1.it

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ORCID iDs
Francesca Romana Spinelli http://orcid.org/0000-0003-1969-2097
Fulvia Ceccarelli http://orcid.org/0000-0001-5026-8783

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Rituximab for granulomatosis with polyangiitis in the pandemic of covid-19: lessons from a case with severe pneumonia

In the pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease 2019 (covid-19),[1 2] the preliminary experience reported by Monti S and colleagues[3] suggests that patients with chronic arthritis (rheumatoid arthritis and spondyloarthritis) receiving bDMARDs (biologic disease-modifying anti-rheumatic drugs) or tsDMARDs (targeted synthetic DMARDs) may not exhibit an increased risk of severe covid-19. These data must be strengthened and confirmed at a larger scale, but remain positive in this drastic context. The authors rightly recommend a continuous surveillance of patients under immunosuppressants, especially since data are lacking in many systemic autoimmune/inflammatory diseases. Notably, anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a group of vasculitides that can involve the respiratory tract (upper and lower airways) and the recent outbreak of covid-19 raises many specific questions concerning the severity of viral infection in AAV patients as well as the therapy with rituximab. Indeed, rituximab, a monoclonal antibody targeting CD20, has become the cornerstone of treatment in the last decade, but is responsible for long-lasting B-cell depletion and potentially severe infectious events (IE) independently from covid-19.[4] A recent observation from our centre illustrates some specific issues with this drug.

A 52-year-old woman was followed for granulomatosis with polyangiitis since 1988 (ear, nose and throat (ENT), orbital, lung, joint and skin involvements, proteinase3 (PR3)-ANCA). She previously received cyclophosphamide (total cumulated dose=41 gr), anti-tumour-necrosis factor agents, mycophenolate mofetil, methotrexate, leflunomide, rituximab and glucocorticoids. Her main comorbidities were overweight (body mass index: 27.05 kg/m2) and hypertension treated with nebivolol. In September 2019, the vasculitis relapsed (arthralgias, ENT, intermittent haematuria and increased PR3-ANCA levels). Four infusions of rituximab (375 mg/m2) were weekly administered in October 2019. The patient improved, and a maintenance therapy with rituximab (500 mg) was administered on 5th March 2020, while she was still under prednisone 15 mg daily. On 6th March 2020 (Day #0), the patient had headaches and myalgias, followed by a 39°C fever and non-productive cough. She was admitted on Day #4 and covid-19 was diagnosed by reverse transcription (RT)-PCR from nasopharyngeal swab specimens. Typical bilateral interstitial pneumonia related to covid-19 was demonstrated on CT scan (figure 1). Other concomitant infections (including pneumocystosis) were excluded. While she remained highly febrile under broad-spectrum antibiotics, the oxygen requirement increased progressively and she presented sudden respiratory failure on Day #18, requiring endotracheal intubation and mechanical ventilation for acute respiratory distress syndrome. Several drugs were given for compassionate use: lopinavir/ritonavir for 3 days from Day #12 and then hydroxychloroquine (200 mg/8 hour) for 10 days from Day #19. The clinical condition improved rapidly, and the patient was extubated (Day #20) and oxygen support was withdrawn (Day #25). Nasopharyngeal RT-PCR were negative twice in the following days and the patient returned home on Day #29.

Until today, immunosuppressive drugs are supposed to be risk factors of severe forms of covid-19. Furthermore, although risk factors are not yet clearly established,[5] our patient had two potential additional ones (overweight and hypertension), making her recovery unexpected. We report herein a severe and life-threatening form of covid-19 in a patient under immunosuppressant, though the worsening occurred more progressively than observed in most series. Both glucocorticoids and rituximab may have limited the cytokine storm and delayed the worsening and need for mechanical ventilation, as compared with previous reports.[2] However, as proposed by Monti and colleagues,[3] we should consider these drugs with caution during the covid-19 pandemic.

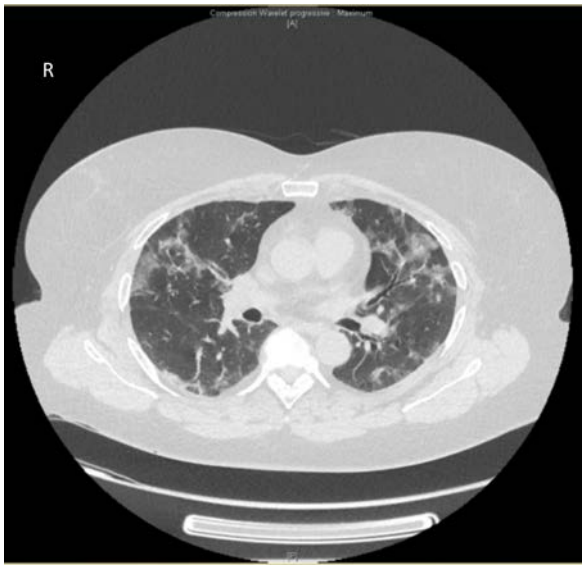

Figure 1 CT scan disclosing ground glass opacities and condensations consistent with a mixed (central and subpleural) pattern of severe covid-19 pneumonia.

Independently from covid-19, infectious events (IE) (mainly pyogenic) may occur in the 3 months following rituximab infusion. Classically, risk factors for infection in patients receiving rituximab include glucocorticoids, other immunosuppressive drugs, diabetes mellitus and age. We previously reported that severe IE were observed in about 25% of patients with autoimmune diseases, and some individuals experienced life-threatening, polymicrobial and opportunistic infections.[4] This frequency was higher than in other studies,[6 7] but this suggests that rituximab may not be as safe as usually supposed, probably depending on the subgroups of treated patients. During covid-19, which may generate an immunocompromised status (as illustrated by lymphopenia and opportunistic infections), the impact of rituximab treatment on IE remains to be clarified. Additionally, the B-cell depletion induced by rituximab reduces the immunogenicity of several vaccines, which encourages to perform vaccination before starting rituximab.[8] Similarly, the immunological memory following SARS-CoV-2 infection will probably be impaired by this biologic, making patients sensitive to a reinfection.

Although we cannot draw any definitive conclusion from our observation, we agree with those who recommend avoiding withdrawal of drugs, because this may lead to relapses of inflammatory diseases. Nevertheless, the specific and long-lasting effects of rituximab make this issue even more delicate and warrant further studies concerning the impact of covid-19 in immunocompromised patients.

Philippe Guilpain,[1,2] Clément Le Bihan,[3] Vincent Foulongne,[4] Patrice Taourel,[5] Nathalie Pansu,[3] Alexandre Thibault Jacques MARIA ,[1,2] Boris Jung,[6,7] Romaric Larcher,[6,7] Kada Klouche,[6,7] Vincent Le Moing[3]

[1]Internal Medicine: Multi-Organic Diseases, Local Referral Center for systemic autoimmune diseases, Saint Eloi Hospital, Univ Montpellier, Medical School, Montpellier University Hospital, Montpellier cedex 5, France
[2]Univ Montpellier, IRMB, Univ Montpellier, INSERM, Montpellier, France
[3]Tropical and Infectious Diseases, Saint Eloi Hospital, Univ Montpellier, Medical School, Montpellier University Hospital, Montpellier cedex 5, France
[4]Pathogenesis and Control of Chronic Infections, Inserm, Universite Montpellier 1 Faculte de Medecine Montpellier-Nimes, Montpellier, Languedoc-Roussillon, France
[5]Osteoarticular Medical Imaging Section, Department of Medical Imaging, University Hospital Centre Montpellier, Montpellier, Languedoc-Roussillon, France
[6]Department of Intensive Care Medicine, Lapeyronie Hospital, Univ Montpellier, Medical School, Montpellier University Hospital, Montpellier, France
[7]Inserm, CNRS, PhyMedExp, Univ Montpellier, Montpellier, France

Correspondence to Dr Alexandre Thibault Jacques MARIA, Internal Medicine: Multi-Organic Diseases, Local Referral Center for systemic autoimmune diseases, Montpellier University Hospital, Univ Montpellier, Medical School, Montpellier cedex 5, France; a-maria@chu-montpellier.fr.fr and Dr Philippe Guilpain, Internal Medicine: Multi-Organic Diseases, Local Referral Center for systemic autoimmune diseases, Montpellier University Hospital, Univ Montpellier, Medical School, Montpellier University Hospital, Montpellier, France; p-guilpain@chu-montpellier.fr

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ORCID iD
Alexandre Thibault Jacques MARIA http://orcid.org/0000-0002-0868-5804

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Diagnostic and therapeutic challenges for patients with ANCA-associated vasculitides at the time of COVID-19. Response to: 'Rituximab for granulomatosis with polyangiitis in the pandemic of COVID-19: lessons from a case with severe pneumonia' by Guilpain *et al*

We thank Dr Guilpain *et al*[1] for their comment regarding the case of a patient with granulomatosis with polyangiitis who developed signs of systemic acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection shortly after having received treatment with rituximab. The comment raises a series of important points of discussion. The differential diagnosis between infectious complications or manifestations of the underlying rheumatological condition has always been a challenge when managing patients with systemic diseases such as antineutrophil cytoplasmic antibody-associated vasculitis (AAV) or connective tissue diseases (CTD). The clinical picture and laboratory and imaging findings in patients with AAV or CTD are often non-specific and need to be differentiated from changes caused by treatment or by infectious complication.[2–4] SARS-CoV-2 has been associated with clinical manifestations and complications that can resemble some changes found in AAV or CTD. The cardiovascular risk, including the risk of deep venous thrombosis and pulmonary embolism, is increased also in AAV and several types of CTD, especially during phases of active disease, and continuous surveillance is mandatory.[5 6] This holistic, multidisciplinary clinical thinking process should always be applied when managing patients with AAV, even in a confirmed case of COVID-19, as correctly described by Guilpain *et al*.[1] Furthermore, the authors hypothesised that treatment with glucocorticoids and rituximab might have delayed the occurrence of severe respiratory failure requiring mechanical ventilation in this patient compared with previous reports. Although this is a possibility, it is also likely that the intensive immunosuppressive regimen, particularly with a drug impairing B lymphocytes, and antibody production response might have played a significant role in the progressive worsening of the clinical conditions of the patient. There are several immunomodulatory treatment options, some with promising results, being tested for COVID-19 mainly targeting key proinflammatory cytokines or pathways, such as the interleukin (IL)-6, IL-1 or Janus Kinase-signal transducer and activator of transcription (JAK-STAT) signalling. However, it is conceivable that while some immunosuppressive agents routinely used for rheumatological conditions might offer an advantage on the exaggerated immune response and cytokine storm being triggered by SARS-CoV-2 in some individuals, other agents, including those acting on cells responsible for antibody production, would actually turn out to be particularly detrimental in the course of COVID-19. Rituximab is a drug with pleyotropic effects on the immune system, with the most prominent being the long-lasting reduction or abrogation of the humoral response by depleting antibody-producing B cells. The ultimate effect of the treatment with rituximab is the reduction of autoantibody production, but on the other hand this can expose the patient to an impaired response to infections and vaccines. Although further studies are needed, it is plausible from the biological effects of rituximab that this drug could interfere with the ability of the subject to properly and rapidly respond to SARS-CoV-2 infection. The hypothesis that a prompt and efficient antibody production against the infection would lead to better outcomes and faster resolution of COVID-19 was used as the rationale for an ongoing experimental treatment study at our hospital (ClinicalTrials.gov identifier NCT04321421) using hyperimmune plasma, rich in IgG against SARS-CoV-2 obtained from recovered patients. Nevertheless, there have also been reports on experimental models in coronaviruses infections suggesting that, again, an excessive reaction to the virus with high levels of anti-spike IgG production would actually contribute to the severity of the disease rather than accelerating its resolution.[7] The comment from our French colleagues[1] offers the grounds to underline once more the complexity of applying immunosuppressant treatments, usually used to treat rheumatological diseases, to a different condition, showing a striking interplay between infectious, inflammatory and immunological pathogenetic mechanisms that are still largely unknown.

Sara Monti , **Carlomaurizio Montecucco**

Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Correspondence to Dr Sara Monti, Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia 27100, Italy; sara.saramonti@gmail.com

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ORCID iD

Sara Monti http://orcid.org/0000-0002-1800-6772

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