EMJ RHEUMATOLOGY

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+ EULAR E-CONGRESS 2020

Reviewed

+ EDITOR'S PICK

Methotrexate and The Lung in Rheumatoid Arthritis

+ INTERVIEWS

Dr Rikke Helena Moe and Ms Sue Oliver OBE talk to us about their experiences as the Chair of the EULAR Standing Committee of Health Professionals in Rheumatology.

+ ABSTRACT REVIEWS

Topics include joint replacement surgery in axial spondyloarthropathy, predicting rheumatoid arthritis, and an update of the EULAR/ERA-EDTA recommendations for management of lupus nephritis.

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Spencer Gore, CEO

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Aims and Scope

EMJ is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

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Welcome

Dear Readers,

It is with great pleasure that I welcome you to another captivating edition of *EMJ Rheumatology*. Within these pages, you will be received by some of the latest, trailblazing research in the field. The COVID-19 pandemic presents unique societal challenges, in particular for medical professionals and it is without doubt that these healthcare heroes have been working their hardest for patients on the front-lines and behind the scenes. Here at EMJ, we aim to facilitate these efforts by providing topical and stimulating content for our valued readers to ensure continued dissemination of academic studies. We hope to promote ground-breaking research through our continuous offering of quality content, including the following pages of *EMJ Rheumatology 7.1*.

Despite cancellation of the face-to-face annual congress, the EULAR 2020 E-Congress truly lived up to its usual expectations and provided an unchallenging virtual congress experience. Our Congress Review section offers an overview of the latest research trends in the field including the effectiveness of rheumatology healthcare professional redeployment and the increased risk of thrombosis in rheumatoid arthritis (RA) patients.

You will also find a review of some of the fascinating abstracts presented at the meeting, with topics ranging from improving risk-stratification of patients with RA for interstitial lung disease to understanding joint replacement surgery in axial spondyloarthropathy. Furthermore, our Congress Session Review on EULAR COVID-19 recommendations written by our gifted editorial staff is a personal recommended read to all wanting to stay up to date.

To complete the full congress experience, make sure to read our interviews with leading EULAR committee member Dr Rikke Helene Moe and past committee member Ms Sue Oliver OBE, who provide an overview of their contributions to the field.

Within these pages, you will also discover an assortment of truly intriguing articles that range from the association between bone microarchitecture and RA to using audiometry to track atherosclerosis. Finally, I would like to acknowledge all contributors and my fantastic EMG-Health team. We hope that you enjoy the topic diversity in the following pages, and we look forward to connecting with you in person at the next face-to-face EULAR congress.

Spencer Gore

Chief Executive Officer, EMG-Health

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Foreword

Dear colleagues,

In my 7th year as Editor-in-Chief, it is my pleasure to welcome you to the 7th volume of *EMJ Rheumatology*. Presented within are a variety peer reviewed articles, the European League Against Rheumatism (EULAR) 2020 congress abstract summaries and full congress review, and interviews with key opinion leaders.

My Editor's Pick is the paper "Methotrexate and The Lung in Rheumatoid Arthritis" by Conway et al. Rheumatoid arthritis (RA) is a common autoimmune chronic inflammatory rheumatic and musculoskeletal disorder (iRMD). Methotrexate (MTX) is the gold standard therapy but it has side-effects including neurotoxicity, anaemia, gastrointestinal discomfort, and MTX-induced pneumonitis (MTX-pn). However, RA patients can develop interstitial lung disease (ILD), which is similar to MTX-pn within 2 years of disease onset if not optimally treated. Conway et al. discuss the risk factors associated with MTX-pn and ILD, and the treatment options with rituximab, tocilizumab, abatacept, antifibrotics, and glucocorticoids. However, recent evidence shows increased risk of ILD worsening in patients treated with biodrugs. It has been shown that activation of JAK2 kinase promotes fibrosis. My view, based on the current knowledge of the physiology of inflammation, is that the time has come to consider using JAK2 kinase inhibitors such as baricitinib early in RA rather than MTX and/or biologics to mitigate risks of ILD development.

Other review topics include chronic inflammation causing osteoporosis via TNFα/IL-1β-mediated RANKL activation. Bone health assessment in RA is there important. Dennison et al. report their findings on high-resolution CT studies of trabecular bone in RA.

Additionally, the role of the anti-inflammatory vitamin D molecule in axial spondyloarthritis (AxSpA) and audiometry to track atherosclerosis are reviewed by Brown et al.

Manica et al. then discuss the historical diagnostic criteria of AxSpA, treat-to-target recommendations, and how the historic diagnostic classification of AxSpA limits early therapy with biologics.

Finally, Greenwald et al. introduce the advances in scleroderma pathophysiology driving novel therapeutic approaches. Hence the boundaries for disease remission continue to be extended in several iRMD.

I am very pleased to present this 7th edition of *EMJ Rheumatology* and thank all the authors and peer-reviewers for committing time to this edition despite the Covid-19 crisis.

With kind regards,

Prof Ian C Chikanza

St Bartholomew's and The Royal London Hospital, UK

Congress Review

Review of the European League Against Rheumatism (EULAR) 2020 E-Congress

Location: EULAR 2020 E-Congress

Date: 3rd June– 6th June 2020

Citation: EMJ Rheumatol. 2020;7[1]:10-18. Congress Review.

FOUNDED in 1947, The European League Against Rheumatism (EULAR) has held its annual conference since the year 2000, successively welcoming thousands of delegates from across the globe to the largest European-based meeting focussed on rheumatic and musculoskeletal disorders. The meeting was due to be held in Frankfurt, Germany on 3rd–6th June; however, no flights to Frankfurt, the largest airport in Germany, were boarded by EULAR delegates this year. The COVID-19 pandemic forced the organisation to bring the meeting to a virtual setting and saw delegates swapping their luggage and passports for headsets and computers.

The meeting always has been, and this year it continued to be, a celebration of scientific advances and updates from the forefront of rheumatology. The opening plenary session was hosted by Prof Iain McInnes, EULAR President, Glasgow, UK, who began by addressing the current state of affairs, expressing his empathy for those who have lost loved ones to COVID-19 and acknowledging that rheumatologists, as healthcare professionals, have all been affected in the fight against the virus. In his introductory remarks, Prof McInnes acknowledged the challenges associated with the late cancellation and the achievements of the society in hosting this new form of meeting when introducing the E-Congress: "Bringing a virtual congress into reality is no mean feat and to the secretariat in the EULAR office, I can only offer my most sincere thanks."

Prof McInnes went on to commend the cutting-edge research that is being rapidly undertaken in the current climate. While there was no opportunity to meet colleagues in person this year, Prof McInnes confidently assured his peers that the quality of the content and learning opportunities remained undiminished, "superb, and informed." He touched on the community of three pillars in the rheumatology society: scientific societies, healthcare professionals, and patients, who together are committed to making a difference to people with

rheumatic and musculoskeletal diseases, and this year's E-Congress did not curb these achievements.

On Day 1 of the E-Congress, EULAR saw 17,500 participants in attendance and many active on social media channels such as Twitter and LinkedIn. The late-breaking abstracts were rigorously reviewed by a EULAR panel of experts, who typically receive over 4,000 abstract submissions per year. Prof Loreto Carmona, Chairperson of the Abstract Selection Committee, Madrid, Spain, gave the list of first authors of scientific abstracts submitted to EULAR who were honoured with an award for the highest quality abstracts.

Given the virtual format of the congress, all resources were made available electronically and will be accessible online until Autumn of this year. The sessions were either recorded live discussions, giving rise to virtual interaction between the speakers and the audience using questions and answer textboxes, or they were provided as prerecorded sessions. Recordings of each session were made accessible via the E-Congress platform after each session.

The congress presented the latest medical news in rheumatology on topics such as the shortages of rheumatologists in Germany, resulting in inadequate treatment for its citizens; the impact of immunosuppressants on the risk of hospitalisation with COVID-19 for patients with rheumatic diseases; and growing opioid use in Europe for pain caused by rheumatological conditions. Highlights of the scientific programme shared by Prof John Isaacs, the EULAR Scientific Committee Chair, Newcastle, UK, included the EULAR COVID-19

"Innovation is at the centre of what is trying to be achieved at EULAR,"

recommendations, the latest advancements in IgG4 disease, treat-to-target approaches in children and adults, high-intensity interval training in patients with rheumatic and musculoskeletal diseases, and artificial intelligence and osteoarthritis.

Mr Claudiu Leverenz, cofounder of Glasschair, Munich, Germany, was invited to speak in the opening session and gave an example of an individual with decreased mobility caused by multiple sclerosis, explaining how their options for increased mobility are largely mechanical. He commented on technological advancements in this age and the importance of finding solutions based on patient engagement and needs. For example, robotic control systems, such as the exoskeleton, are exciting machines designed to allow individuals to control their home environment and perform daily tasks without using parts of the body impacted by disease. Mr Leverenz emphasised the potential of modern technology for giving more independence to people with a disability, the importance of engaging with technology in the current situation we are in, and the need to engage patients at the beginning of the innovation process.

Prof McInnes addressed his virtual audience and agreed with Mr Leverenz's plea: "Innovation is at the centre of what is trying to be achieved at EULAR," as it becomes increasingly clear this year that in medicine, "content has been brought into the electronic universe."

"Bringing a virtual congress into reality is no mean feat and to the secretariat in the EULAR office, I can only offer my most sincere thanks."

Effectiveness of Rheumatology Healthcare Professional Redeployment

SHORTAGES of rheumatologists has meant that only half of patients with inflammatory-rheumatic disorders in Germany receive adequate treatment. To reduce waiting times and prevent patient health deterioration, German researchers are suggesting care of patients with rheumatic diseases by 'rheumatological assistants' is just as effective as care by specialist rheumatologists, as evidenced by a recent study.

This was announced in a press release at the EULAR 2020 E-Congress on 3rd June 2020.

It is already a well-established practice in other European countries for rheumatological assistants, such as paramedics, nurses, and student nurses, to be redeployed to rheumatic care. To examine its viability in the German healthcare system, a prospective, randomised, controlled, multicentre study was conducted. 236 patients participated in the study after confirmation of rheumatoid arthritis was confirmed via a blood test. The average age was 58 years, the average number of months since diagnosis was 130, and >70% were female.

The participants were treated for a 12-month period, whereby one group were treated exclusively by rheumatologists and the other group by a combination of rheumatologists and rheumatological assistants. The patients' condition was measured using the Disease Activity Score at 28 joints (DAS28); those who were treated by rheumatological assistants scored an average of DAS28 2.43, whereas the group treated by rheumatologists was DAS28 2.29.

EULAR President Prof Ian McInnes from Glasgow, UK, declared that "this difference is not clinically or statistically significant."

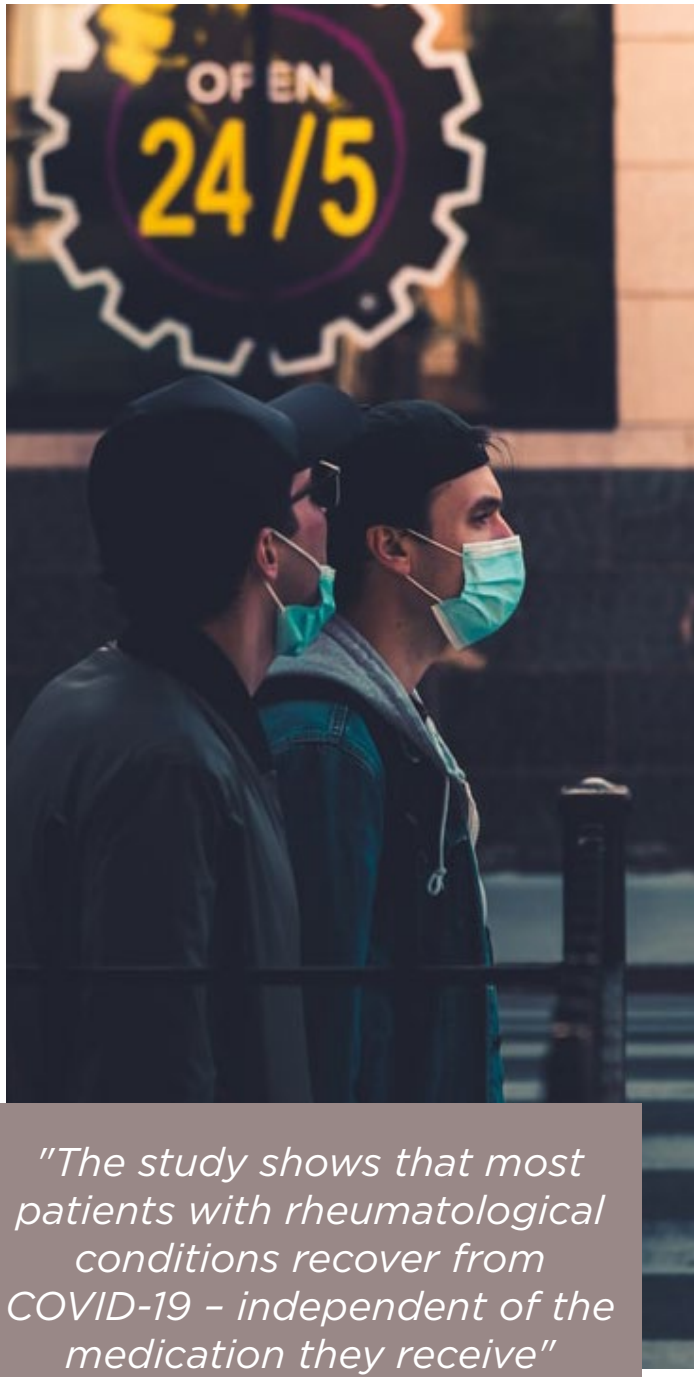
Approximately 2% of the adult German population is affected by chronic inflammatory rheumatic diseases, equating to at least 1.5 million people. Patients often present with severe pain, fatigue, stiffness, and lack of strength, which can have a significant impact on their daily activities, education, career, and family.

"the existing medical resources do not suffice to provide early, patient-centred, and guideline-based care."

Dr Kirsten Hoeper of the Hanover Medical School, Hanover, Germany, and lead author of the study, explained that "the existing medical resources do not suffice to provide early, patient-centred, and guideline-based care."

Dr Hoeper and Prof McInnes both conclude that rheumatological assistants will ultimately lead to better patient care in a very cost-effective way.

Hospitalisation Vulnerability Caused by Immunosuppressants for Rheumatic Diseases



"The study shows that most patients with rheumatological conditions recover from COVID-19 – independent of the medication they receive"

VULNERABILITY to severe and opportunistic infections, such as COVID-19, is a risk of immunosuppressive therapies. A study has determined the impact of these immunosuppressants on the risk of hospitalisation with COVID-19 for patients with rheumatic diseases.

The Swiss study, presented at the EULAR 2020 E-Congress on 3rd June 2020, considered case data of 600 patients with rheumatic disease and COVID-19 from 40 countries, using the combined EULAR and Global Rheumatology Alliance COVID-19 registries. The cases from 24th March to 20th April 2020 included details of age, sex, smoking status, rheumatic disease diagnosis, comorbidities, and antirheumatic therapies taken immediately prior to infection.

Conventional disease-modifying antirheumatic drugs (DMARD), including antimalarials and methotrexate, and nonsteroidal anti-inflammatories (NSAID) were not associated with hospitalisation, including DMARD treatment in combination with biologics, such as TNF-α inhibitors. Monotherapy with TNF-α inhibitors was associated with a reduced risk of hospitalisation. Treatment with prednisolone >10mg daily increased the probability of hospitalisation.

The study analysed cases of known COVID-19 in patients with rheumatic diseases; it does not describe the risk of contracting COVID-19 infection and, because of likely increased reporting of severe cases, is biased toward reflecting these more-severe cases. Overall, 46% of patients studied required hospitalisation, with a total mortality rate of 9%.

"The study shows that most patients with rheumatological conditions recover from COVID-19 – independent of the medication they receive," says Prof Dr John Isaacs, Scientific Chair of the EULAR Scientific Committee. "It is necessary, however, to gather more knowledge about the course of an infection with the novel coronavirus in patients with inflammatory rheumatic conditions."

To address this need for insight, the global rheumatologist community rapidly set up an international COVID-19 registry (www.rheum-covid.org), which was then mirrored by a EULAR COVID-19 registry; these registries were the source of data for this study. Ongoing global engagement with, and analysis of, these registries will support the ongoing care of patients with rheumatic diseases during the current COVID-19 pandemic.

Increasing Opioid Use in Patients with Osteoarthritis

GROWING opioid abuse in Europe calls for measures to use these analgesics more safely. That is according to findings from a study presented at the EULAR 2020 E-Congress in a press release dated 3rd June 2020. A growing number of individuals have been found to take opioid drugs such as fentanyl, tramadol, or tilidine for pain caused by rheumatic and musculoskeletal disease.

The researchers used the Information System for Research in Primary Care (SIDIAP) health database with records from approximately 6 million people in Catalonia, Spain, to provide information on opioid consumption in patients with osteoarthritis and the associated growing risks in Europe. Opioids are strong analgesics that cause side effects such as nausea, vomiting, chronic constipation, dizziness, and fatigue, and affect the central nervous system, posing a large risk for the individual. The effect on the nervous system accounts for their strong addiction potential and difficulty with withdrawal from the drug.

The study showed that opioid consumption increased from 15% to 25% between 2007 and 2016. The groups associated with greater risk included females, who were shown to be 4% more affected than males; older patients, who were 10% more affected than younger patients; people living in rural areas, who had a 1% increased risk compared to those from urban areas; and individuals at a 'social disadvantage,' who had a higher risk than those with a higher socioeconomic status. The lead author of the study, Dr Junqing Xie from the University of Oxford, Oxford, UK, commented: "Taking opioids, in particular strong opioids, has substantially increased in recent years in patients newly suffering from osteoarthritis." The researchers highlighted the need for urgent precautions to ensure safe prescribing and administration of this type of medication.

"Taking opioids, in particular strong opioids, has substantially increased in recent years in patients newly suffering from osteoarthritis."

Increased Risk of Thrombosis in Rheumatoid Arthritis Patients

THROMBOSIS poses a significant medical problem, particularly in the case of venous thromboembolism (VTE) where clotting inside blood vessels affects the blood flow. According to findings from two studies presented in a press release at the EULAR E-Congress 2020, on 5th June, individuals affected by rheumatoid arthritis (RA) with increased disease activity have a higher risk of thrombosis. However, this risk can be reduced by treatment with biological disease-modifying antirheumatic drugs (bDMARD).

The risk of deep vein and pulmonary thrombosis is 2–3 times higher in patients with RA as a result of the immune system turning against the body and causing chronic inflammation, which in turn can have a disruptive effect on coagulation.

A Swedish Cohort study explored whether the degree of disease activity correlated with the risk of thrombosis by analysing data of 46,311 patients with RA taken from the Swedish Rheumatology Quality Register (SRQ) over a period of 12 years. The Disease Activity Score 28 (DAS28) describes the severity of RA based on the assessment of 28 defined joints. Results indicated a close connection between RA disease activity measured by DAS28 and the risk of VTE. Viktor Molander, PhD student, Karolinska Institutet, Stockholm, Sweden, stated: "Among patients with high disease activity, 1 in 100 is going to develop VTE within the following year, a more than two-fold increase compared to patients in remission."

Because the risk of thrombosis may also be influenced by the medication used to treat RA, a German study investigated whether the risk of thrombosis is reduced when using a bDMARD such as TNF inhibitors in comparison to conventional synthetic DMARD (csDMARD). Analysis of data from >11,000 RA patients from the German RABBIT1 register who were treated with another csDMARD after at least one csDMARD failure, or whose treatment was switched to bDMARD, showed that treatment with TNF inhibitors reduced the risk of VTE by half compared to csDMARD treatment.

Further RABBIT data showed an association between increase in inflammatory activity and risk of VTE. These results showcase the importance of regular check ups by a rheumatologist to monitor the condition and adjusting treatment accordingly.

"Among patients with high disease activity, 1 in 100 is going to develop VTE within the following year, a more than two-fold increase compared to patients in remission."

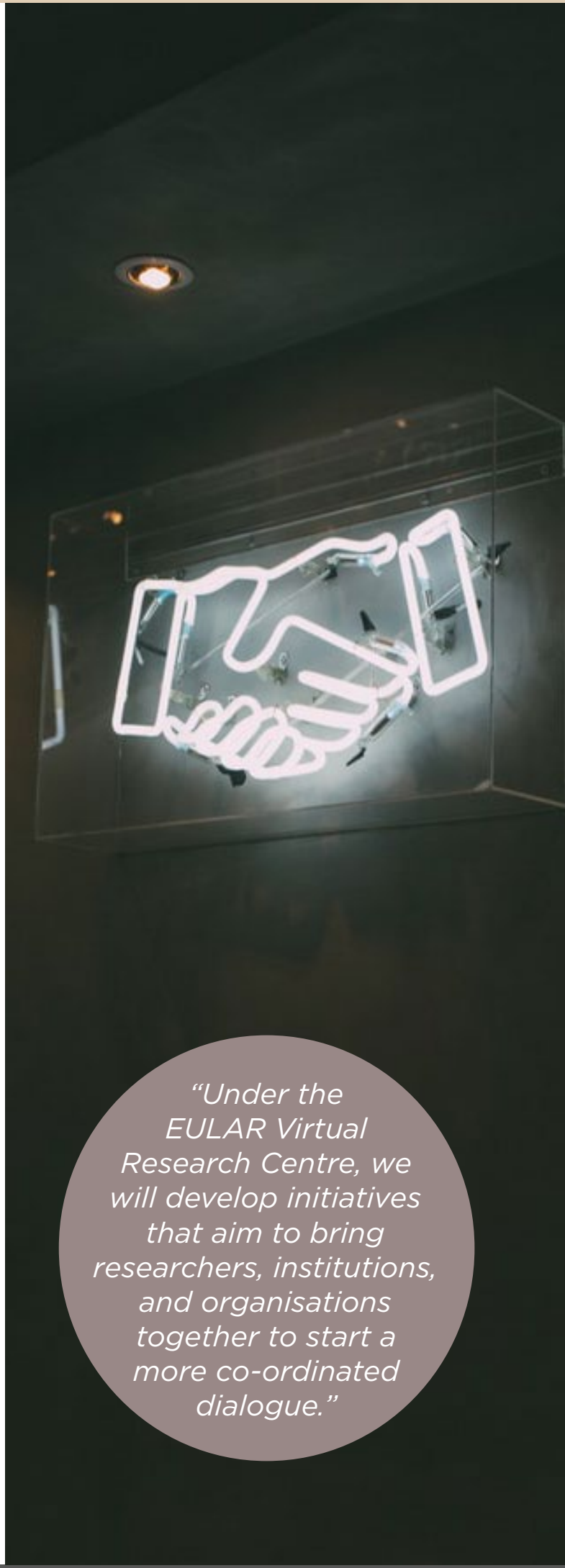
EULAR Virtual Research Centre Launched to Accelerate Rheumatic Disease Research

RESEARCH and innovation are integral to the progression of disease characterisation and the development of prevention and treatment strategies. With millions of people worldwide living with rheumatic diseases that severely affect their everyday life, many of which the cause is unknown and without curative therapies, it is important to develop effective treatment approaches. In addition to their many contributions to achieving this goal, in a press release from EULAR 2020, dated 9th June 2020, it was announced that EULAR have launched the Virtual Research Centre.

Many barriers exist in the research landscape of rheumatic and musculoskeletal diseases, meaning that comprehensive and co-ordinated actions at the European Union (EU), national, and regional level are required, in addition to policy areas such as public health, healthcare, and employment and social affairs, commented EULAR President Prof Iain McInnes, University of Glasgow, Glasgow, UK. The new EULAR Virtual Research Centre will provide the platform to overcome such barriers and facilitate collaboration between basic, clinical, and translational research in rheumatology.

Specifically, unmet needs in research are highlighted in the centre's research roadmap. Additionally, research resources, infrastructure, services, and training will also be incorporated, promoting the opportunity to conduct first-rate, interdisciplinary rheumatic and musculoskeletal disease research.

Prof McInnes explained: "Under the EULAR Virtual Research Centre, we will develop initiatives that aim to bring researchers, institutions, and organisations together to start a more co-ordinated dialogue." In addition to facilitating the identification of prevention strategies, risk factors, methods of early diagnosis, and potential therapies in rheumatology, the platform also has the ability to alleviate disease burden of conditions that often concur with rheumatic diseases, such as heart disease, diabetes, cancer, Alzheimer's disease, and depression.



"Under the EULAR Virtual Research Centre, we will develop initiatives that aim to bring researchers, institutions, and organisations together to start a more co-ordinated dialogue."

EULAR COVID-19 Recommendations

Rachel Donnison
Editorial Assistant

Citation: EMJ Rheumatol. 2020;7[1]:19-21.

TREATING patients with autoimmune diseases, the rheumatology community is naturally concerned with the spread of COVID-19; as Prof Robert Landewé of the University of Amsterdam, Amsterdam, the Netherlands stated: "immunosuppression and infection do not go along very well." On April 3rd 2020, EULAR President-Elect Prof Hans Bijlsma founded a task force to create a comprehensive set of guidelines for clinicians treating patients with rheumatic disease and COVID-19, though not in a typical manner. Using Microsoft Teams and teleconferences, the newly founded committee set out to create a comprehensive set of recommendations. Time was of the essence, as the virus continued to spread and rheumatologists looked to EULAR for guidance. Exactly 3 months later the guidelines were presented at the EULAR 2020 virtual congress on 3rd June 2020.

PROVISIONAL RECOMMENDATIONS

Musculoskeletal disease guidelines in the context of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), as outlined by EULAR, is "an unprecedented set of recommendations," according to Prof Landewé. In a pandemic, EULAR's usual methodical approach to finalising recommendations, which takes at least 12–18 months, had to be significantly shortened; the stages of consensual approach and systematic literature research were forgone as there was no literature or evidence to guide them.

The recommendations for patients with rheumatic disease and COVID-19 start with five overarching principles:

1. There is no evidence that these patients are more at risk of contracting SARS-CoV-2, nor do they have a worse prognosis if they are infected.

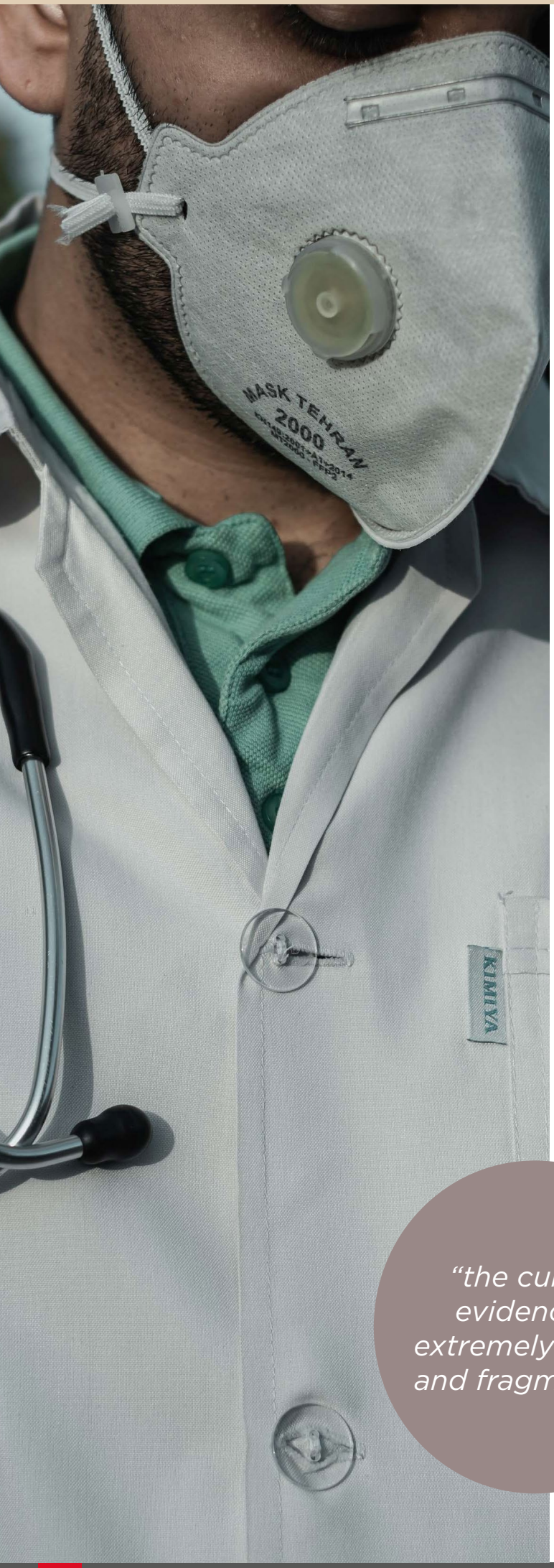
2. Diagnosis and treatment of patients is the primary responsibility of an expert in treating COVID-19 (e.g., a respiratory physician or infectious disease specialist).

3. Decisions based on immunosuppressive treatment (e.g., disease-modifying antirheumatic drugs [DMARD]), maintenance, or discontinuation should involve rheumatologists.

4. Rheumatologists should be involved in local, regional, or national guideline committees regarding use of DMARD, the use of which should be a multidisciplinary decision.

5. Off-label use of DMARD in COVID-19 outside the context of clinical trials should not be encouraged.

Prof Landewé concluded by highlighting "the current evidence is extremely sparse and fragmented" and that as a task force they are "flying blindly," whilst also following many jurisdictions within Europe, with many conflicting opinions.



ACR RECOMMENDATIONS

The American College of Rheumatology (ACR) recommendations were subsequently presented by the Chair of the ACR COVID-19 Clinical Task Force Prof Ted Mikuls of the University of Nebraska Medical Center, Omaha, Nebraska, USA. To accommodate the changing literature and evidence landscape regarding the virus, the ACR task force has committed to a monthly update of the recommendations, compared to EULAR's quarterly pledge. Voting initially on 81 statements, of which 77 were approved, the team combined these into a list of 25 guidance statements, compared to EULAR's 13.

The ACR recommendations are divided into three groups, the first being guiding principles with a primary focus on the patient and provider level, based on the sparse but rapidly evolving evidence. The second grouping of ACR guidance concentrates on stabilising patients: "In the absence of known exposure and the absence of COVID-19 infection, our panel felt very strongly about the importance of continuing rheumatic disease treatments," conveyed Prof Mikuls. The overarching theme of this second group was the potential risk that unchecked inflammation and rheumatic disease posed to patients with COVID-19.

Finally, the third grouping provided guidance to physicians for patients with known exposure or presumed infection of SARS-CoV-2. Prof Mikuls was careful to point out that "our recommendations suggest at least temporary discontinuation of most immunosuppressive and biologic medications" while patients recover from infection.

Though tasked with describing the differences between the EULAR and ACR recommendations, Prof Mikuls found the similarities reassuring: "we're approaching the unknown from very different parts of the world, and arriving in a very similar place."

"the current evidence is extremely sparse and fragmented"

"we're approaching the unknown from very different parts of the world, and arriving in a very similar place."

MAPPING THE EVIDENCE OF A NEW DISEASE

Critical situations, such as the COVID-19 pandemic, spark many questions in need of answers, explained Dr Féline Kroon of Leiden University Medical Centre, Leiden, the Netherlands. Beginning with a discussion of the literature on COVID-19, Dr Kroon used the case of hydroxychloroquine for the treatment of COVID-19. *In vitro* studies initially showed that the drug may be beneficial to those infected with COVID-19, leading to its incorporation into many clinical protocols as some physicians embraced the opportunity of a potential treatment.

"Oversimplification and also quick dissemination of these publications was done in the lay press and social media," leading to shortages of the drug to patients with rheumatic diseases, relayed Dr Kroon. Hydroxychloroquine has now been associated with risk of serious adverse events and the first controlled clinical trials have not been able to confirm its efficacy.

From January 1st–May 22nd 2020 there has been an exponential increase in publications on PubMed relating to the search terms "COVID-19 AND rheumatic diseases OR drugs used in rheumatic diseases". Dr Kroon analysed the search results and found that most publications were viewpoints or narrative reviews and contained no original data, and that the number of clinical trials was, in fact, negligible.

Of the 23 studies published between April 2nd and May 20th using the aforementioned search terms, 13 were cohort studies and 10 were case studies (including case reports and case series). Looking at the 10 case studies, the majority assessed hospitalised patients and the median number of patients was one, whereas in the 13 cohort studies the median number of patients was 165, most of whom were from the outpatient clinic. The type of rheumatic disease ranged from rheumatoid arthritis to vasculitis, systemic sclerosis, or psoriatic arthritis. Combining both sets of studies, the median percentage of positive COVID-19 patients was 3%.

Taking into account the available data up to this point, the key messages from Dr Kroon were that the publication landscape of patients with COVID-19 and rheumatic diseases is evolving at a rapid pace, and that there is no current, robust evidence strong enough to draw conclusions on the effects of the virus on patients with rheumatic disease.

"It is our responsibility to carefully interpret the study details that do emerge, especially in this digital era," Dr Kroon emphasised in her concluding remarks.

Advancing the Treatment of Psoriatic Arthritis: Focus on the IL-23 Pathway

This Janssen-sponsored satellite symposium took place on 3rd June 2020, as part of the European League Against Rheumatism (EULAR) 2020 E-CONGRESS

Chairperson: Georg Schett[1]

Presenters: Laura C. Coates,[2] Kristian Reich,[3] Georg Schett[1]

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Meeting Summary

This Janssen-sponsored live symposium "Advancing the Treatment of PsA: Focus on the IL-23 Pathway," took place virtually at the European League Against Rheumatism (EULAR) 2020 E-CONGRESS. The presentations focussed specifically on the role of IL-23 in psoriatic arthritis (PsA), including an overview of PsA pathogenesis, updates on the latest treatments, and how insights from recent clinical trials can be applied as individualised treatments in daily clinical practice for patients with PsA.

Prof Reich discussed the role of the IL-23 pathway in psoriatic skin inflammation, highlighting how IL-23 inhibition results in high levels of clinical response in the majority of treated patients with psoriasis and the importance of early treatment for maximal disease modification. Studies are currently ongoing to examine the efficacy of IL-23 inhibition as a treatment option for patients with PsA, and it is likely that IL-17 and IL-23 both have differential roles in the psoriasis and PsA disease domains.

Analyses of clinical trial data, presented by Prof Schett, show that treatment with IL-23 inhibitors results in improved outcomes in patients with PsA, including American College of Rheumatology (ACR) and Psoriasis Area Severity Index (PASI) responses. The results of the DISCOVER-1 and -2 trials with guselkumab show that treatment significantly improved PsA outcomes, including ACR20 responses and resolution of enthesitis and dactylitis, compared with placebo in patients with PsA, solidifying the role of the IL-23 pathway in musculoskeletal diseases.

Dr Coates shared her experiences in optimal patient treatment approaches in PsA, highlighting the heterogeneous nature of the disease and sharing current treatment recommendations. She stressed the importance of personalised, treat-to-target treatment strategies, based on patient needs and disease domains, for optimal PsA management.

A Fresh Look at the IL-23 Pathway in Psoriatic Disease

Professor Kristian Reich

The Pathophysiology of Inflammatory Skin Diseases

Psoriasis is one of the most common inflammatory skin diseases, characterised by hyperproliferation and abnormal differentiation of epidermal keratinocytes, thereby initiating a chain of reactions resulting in skin lesions containing immune infiltrate T cells and dendritic cells.[1] Surface markers such as cluster of differentiation 11C (CD11C), a marker for dendritic cells, and CD3, a marker for T cells, are also colocalised in psoriatic skin.[1] Traditional models of psoriasis postulate that there is a delicate cross-talk between dendritic cells and T cells; cytokine signalling also drives T-cell activation, resulting in overproduction of antimicrobial peptides and cytokines, including IL-12, IL-23, IL-17, and TNFα, among others.[2] However, while previous studies have indicated that IL-23 plays a critical role in psoriasis pathophysiology, there is little evidence indicating that the same is true for IL-12.[3] Psoriatic lesions contain raised levels of genes encoding for both the p19 and p40 subunits of IL-23, compared with genes associated with the p35 unit of IL-12, providing a rationale for the efficacy of IL-23 blockade as a treatment for patients with psoriasis.[3] Studies with briakinumab and ustekinumab, both of which bind to the p40 subunit of IL-12/23, show that treatment results in significantly improved PASI 75, 90, and 100 scores compared with placebo after 12 weeks of treatment.[4-6]

Previous studies have also indicated the role of IL-17 in psoriasis development, showing that increases in IL-17A, IL-17C, and IL-17F create a positive proinflammatory feedback loop in patients with psoriasis.[7] Furthermore, one study found a significant correlation between clinical disease activity, measured via PASI scores, and IL-17A and IL-17F levels in patients with psoriasis.[8] This same study also found that different concentrations of TNFα, IL-17A, and IL-17F were capable of synergistic activation of the antimicrobial peptide human β-defensin-2 production in keratinocytes.[8] Preclinical experiments examining the roles of IL-17A and IL-17F in chronic tissue inflammation found that IL-17F functions as a key driver in chronic tissue inflammation, and that neutralisation of both IL-17A and IL-17F resulted in suppression of inflammation and favourable PsA outcomes.[9]

In a mechanistic study of skin inflammation, IL-17 and TNFα activation resulted in the production of osteoclast progenitor cells and multinucleated cells with increased expression of *NF-ATc1*, which plays a role in RANKL signal transduction and has a direct impact on bone resorption in patients with psoriasis.[10] Therefore, the current psoriasis disease model contains both feed-forward and feed-backward responses, showing how the activation, upregulation, and proliferation of T cells creates a "vicious circle" of increased synergistic proinflammatory effects, increases in innate immunity, and keratinocyte proliferation.[11] In the skin, the cytokine environment regulates leukocyte differentiation into functional subsets; when IL-23 levels increase, inducible IL-17 activation results in the production of pathogenic Th17 cells, while an absence of IL-23 results in the production of the nonpathogenic variant (Figure 1).[12,13]

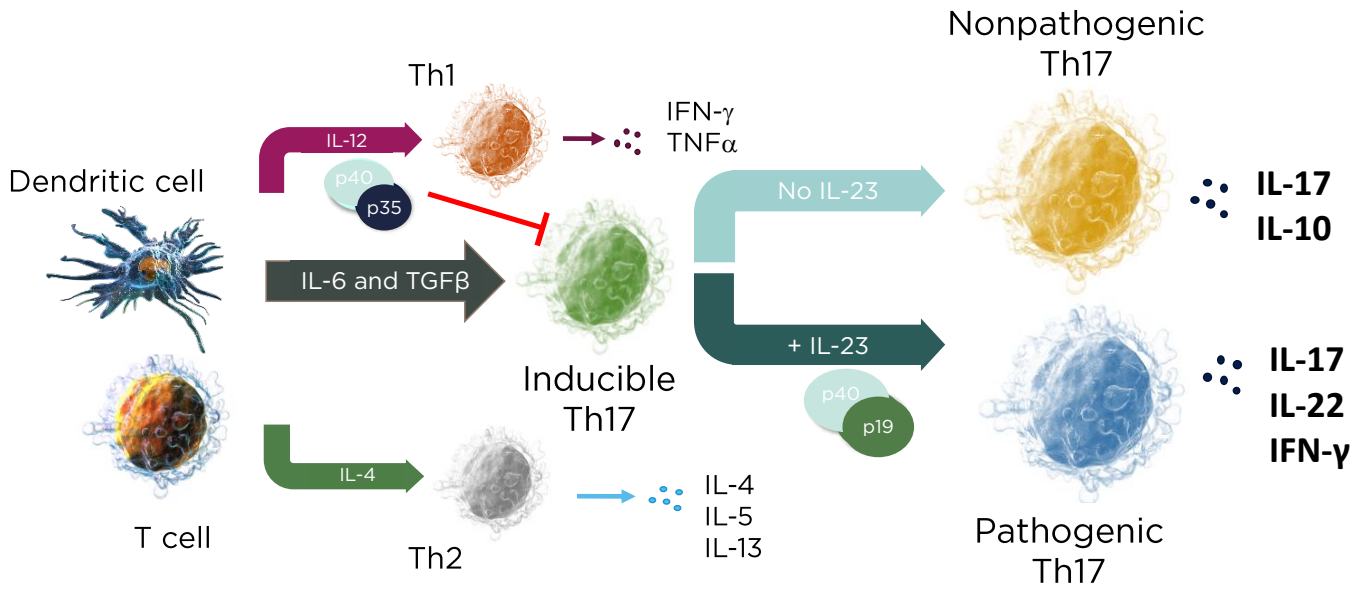

Figure 1: The cytokine environment can regulate lymphocyte differentiation into nonpathogenic and pathogenic subsets.

Adapted from Leung et al.[12] and Zhu et al.[13]

Long-Term Disease Control and Disease-Modifying Potential of IL-23 Blockade

The development of T cells with a tissue-resident memory T (T_{RM}) cell phenotype creates an "inflammatory memory" that develops over time in psoriatic skin. These T_{RM} levels can remain elevated after treatment cessation in patients with clinically nonactive psoriatic lesions, indicating that IL-17 production and possible disease recurrence is maintained by T_{RM} "disease memory" cells.[14,15] Therefore, the targeting of T_{RM} cells may be crucial in achieving long-term disease modification in patients with psoriasis.

In the VOYAGE-2 trials with guselkumab, a monoclonal antibody that specifically binds to the p19 subunit of IL-23, 88.6% and 86.0% of patients with moderate-to-severe psoriasis maintained PASI 90 responses at Weeks 48 and 72 of treatment, respectively. However, this study also showed that 36.8% and 11.5% of patients, respectively, also maintained PASI 90 responses after withdrawal from treatment, indicating that treatment resulted in long-term maintenance of response and a prolonged effect on IL-17-producing cells.[16-18] Maintenance of PASI 90 responses after withdrawal was associated with continued suppression of IL-17A, IL-17F, and IL-22. Guselkumab treatment resulted in cytokine levels that were comparable to healthy controls after 20 weeks of retreatment following withdrawal, while loss of PASI 75 response was associated with increases in serum IL-17A, IL-17F, and IL-22.[17]

The ECLIPSE trial examined the clinical and molecular differences associated with IL-23p19 and IL-17A inhibition with guselkumab and secukinumab, respectively, in patients with psoriasis. Results showed that PASI 90 scores were maintained in 84% of patients receiving guselkumab and 70% of patients receiving secukinumab.[19] An examination of T-cell frequency in psoriatic lesions and psoriatic skin showed that guselkumab treatment significantly reduced the frequency of $CD8^+$ T_{RM} within T cells at Week 24 of treatment, compared with secukinumab.[20] Treatment resulted in reductions in T_{RM} frequency and may subsequently halt the inflammatory cycle, indicating a possible disease-modifying effect.[20] The frequency of regulatory T cells, which play a role in immune-response suppression, was maintained with guselkumab and reduced with secukinumab at Week 24 of treatment.[20] Furthermore, the results of the VOYAGE-1 trial

indicated that guselkumab treatment resulted in substantial proportions of patients maintaining PASI 90 responses from Weeks 52 to 204, further underlining the stable long-term responses associated with guselkumab treatment.[21]

In conclusion, Prof Reich emphasised the key role played by IL-23 in psoriatic skin inflammation, and that inhibition of IL-23 appears to be a safe therapy for patients with psoriasis. Treatment results in high levels of clinical response in the majority of patients, though early treatment, prior to the development of T_{RM} cells, may be the key to prolonged improved responses in patients with psoriasis.

What's New in Targeting the IL-23 Pathway in Psoriatic Arthritis?

Professor Georg Schett

Currently, IL-23 is associated with the pathogenesis of psoriasis and inflammatory bowel disease,[22] with possible involvement in PsA and spondyloarthritis (SpA).[23] However, research performed in the past decade has revealed that different organs show different cytokine patterns in SpA.[23] The inflammatory profile of PsA involves different upregulated cytokines; patients with joint and entheseal disease show increases in IL-23, IL-17, and IL-8, all typically elevated in psoriatic disease, as well as increases in C-reactive protein.[24] IL-23 has been implicated as one of the key mediators of entheseal inflammation, activating inflammatory cytokines, and resulting in increased IL-17A, TNFα, IL-22, and polymorphonuclear neutrophil production, with localised tissue responses.[25-27]

In the ECLIPSA study, patients with enthesis-driven PsA receiving the standard dose of the IL-12/23 inhibitor ustekinumab showed marked improvements in enthesitis outcomes compared with TNF inhibitor treatment. Ustekinumab treatment resulted in improvements in Leeds Enthesitis Index (LEI), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), and Spondyloarthritis Research Consortium of Canada (SPARCC) scores after 6 months of treatment.[28] Suppression of subclinical enthesopathy was also clearly pronounced in patients with psoriasis during the 52-week treatment period.[29]

Several IL-23p19 inhibitors, which have concluded Phase III trials for psoriasis, Phase II trials for PsA, or are currently undergoing Phase III trials for PsA, are in development.[30] Recent Phase II studies have shown that treatment with guselkumab 100 mg every 8 weeks (q8w) for 24 weeks results in ACR20 responses in 58% of patients with PsA, compared with 18% of patients receiving placebo (Δ40%).[31] Similarly, a Phase II study showed that 43% and 48% of patients receiving risankizumab 150 mg at Weeks 0, 4, 8, and 16, and Weeks 0, 4, and 16, respectively, showed ACR20 responses at Week 24, as did 59% of patients receiving doses at Weeks 0 and 12, and 40% patients receiving a single dose of risankizumab 75 mg, compared with 31% of patients receiving placebo (Δ12%, 17%, 28%, and 9%, respectively).[32] Furthermore, 73% and 71% of patients receiving tildrakizumab 20 mg or 100 mg every 2 weeks, respectively, showed ACR20 responses at Week 24, as did 77% and 80% of patients receiving higher doses of 200 mg, given either every 2 or 4 weeks, respectively, all compared with 50% of patients receiving placebo (Δ23%, 21%, 27%, and 30%, respectively).[33]

Speed of Response

Guselkumab treatment is also associated with a rapid onset of action in patients with PsA, as shown by the results of a Phase II study.[31] Patients receiving guselkumab 100 mg q8w showed significant improvements in ACR20 scores as early as Week 4, compared with placebo ($p \leq 0.001$), which was sustained through Week 24 ($p \leq 0.001$), with approximately 60% of patients also showing sustained ACR20 responses from Weeks 24 to 56.[31] Similarly, patients receiving tildrakizumab 200 mg q4w/q12w or 100 mg q12w, or were switched to 200 mg q12w, showed rapid improvements in ACR20 scores during the first 24 weeks of treatment, as did patients who were switched from placebo to tildrakizumab 200 mg q12w at Week 24 of treatment.[34]

Clinical Joint Response

Peripheral joint disease in PsA is characterised by several clinical factors, including IL-23 expression in PsA-related synovitis, and several peripheral joint characteristics, including a mixture of synovitis, enthesitis, and tendinitis. As such, this requires PsA-focussed clinical studies to address a polyarticular disease phenotype.[35-37]

The results of the DISCOVER-2 study, which examined the effect of guselkumab 100 mg q4w or q8w on ACR20 responses in biologic-naïve patients with active PsA, showed that 64.1% and 63.7% of patients achieved the primary endpoint of ACR20 response at Week 24, respectively, compared with 32.9% of patients receiving placebo (p<0.001 for both doses).[38] Both doses were clinically effective at Week 4, compared with placebo (q4w: p<0.01; q8w: p<0.05), with significant differences between both doses and placebo at Week 16, the major secondary endpoint (p<0.001 for both doses).[39] Guselkumab treatment also resulted in sustained effects on peripheral joint disease in the DISCOVER-2 trial, with 74.6% (q8w) and 70.6% (q4w) of patients achieving ACR20 responses at Week 52; similar responses were achieved at the same time point in patients who switched from placebo to guselkumab q4w at Week 24 (Figure 2).[40]

The results from the DISCOVER-1 trial also showed that similar proportions of both biologic-naïve and patients previously treated with TNF inhibitor achieved ACR20 responses at Week 24 of treatment with either guselkumab dose.[41,42]

Resolution of Entheseal Inflammation

Entheseal inflammation, another well-known characteristic of PsA, occurs most frequently in direct connection to the joints, but can also occur at sites distant to the joints.[25] Erosion and enthesophyte production are also hallmarks of radiographic progression in patients with PsA.[43] Patients in the DISCOVER-1 and -2 trials showed significant resolution of enthesitis (p<0.03 for both doses) and dactylitis (q8w: p<0.03; q4w: p<0.01), compared with placebo, at Week 24 of treatment.[38,39] Guselkumab treatment also showed evidence of a disease-modifying effect, slowing radiographic progression, with less joint narrowing and fewer erosions, compared with placebo, at Week 24 of treatment (q8w: p=0.072; q4w: p=0.011).[38,39] The results of the DISCOVER-2 study demonstrated that patients receiving either dose of guselkumab showed significant improvements in PASI scores, with 79.0% (q8w) and 78.3% (q4w) achieving PASI 75 scores at Week 24, compared with 23% of patients receiving placebo (p<0.0001).

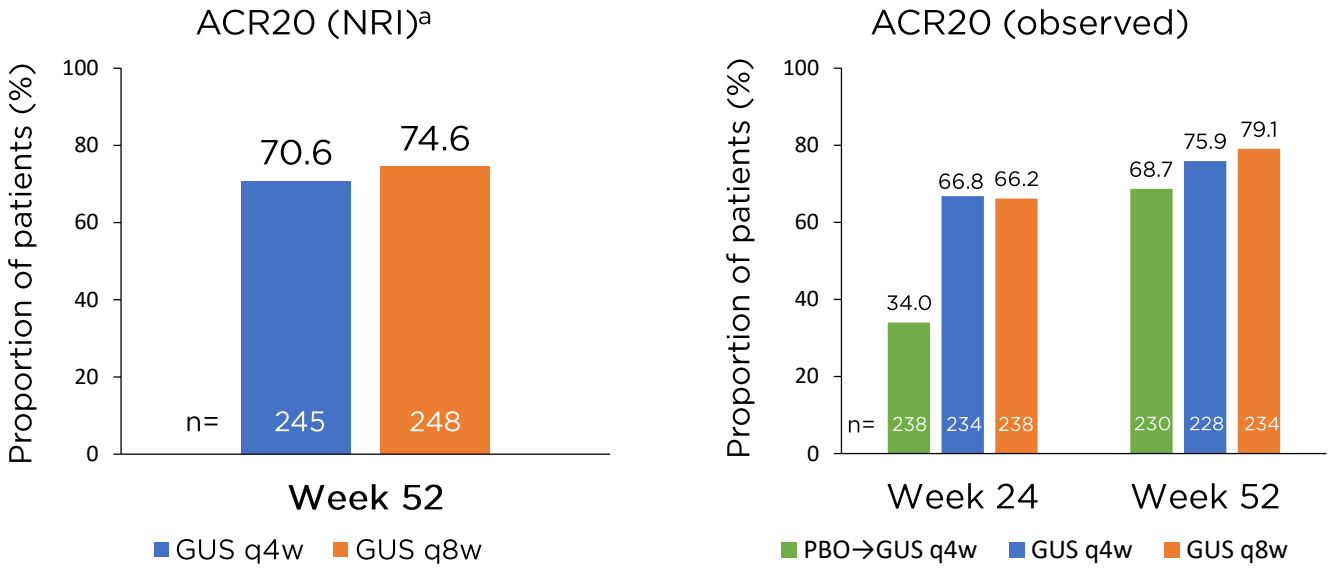

Figure 2: Sustained effect of guselkumab on peripheral joint disease in the DISCOVER-2 study with biologic-naïve patients with psoriatic arthritis.

[a]NRI analysis included patients randomised to q4w and q8w at Week 0 who received at least one dose of study treatment.

ACR: American College of Rheumatology; GUS: guselkumab; NRI: nonresponder imputation; PBO: placebo; q4w: every 4 weeks; q8w: every 8 weeks.

Adapted from McInnes et al.[40]

Similar results were seen for PASI 90 and 100 scores with both guselkumab doses, compared with placebo.[38,39] Both guselkumab doses also resulted in significant improvements in quality of life (QoL) and physical functions scores at Week 24 in patients with PsA.[44] Prof Schett concluded by further underlining that these results solidify the role of IL-23 in immune-mediated inflammatory diseases, including PsA.

Approaches to Personalised Management of Psoriatic Arthritis: Best Practices and Optimised Care

Doctor Laura Coates

The overarching principles of optimal PsA management include concepts such as therapeutic goals; patient, clinical, and comorbidity assessments; treatment individualisation; and prompt assessments of whether these goals are being achieved (Figure 3).[45]

Several factors, including patient preferences, previous treatments, disease severity, disease domains and comorbidities, and PsA domains, play vital roles in patient-specific treatment individualisation.[45] The type of PsA disease activity also plays a role, as patients may present with peripheral arthritis, skin or nail involvement, enthesitis, dactylitis, and axial disease.[45]

The current EULAR PsA treatment recommendations include initial treatment with nonsteroidal anti-inflammatory drugs and local glucocorticoid injections as needed, together with treatment with a conventional synthetic disease-modifying antirheumatic drug. However, these treatments are not currently indicated for enthesitis and patients with predominant axial PsA.[46] Biologic treatments can include TNF, IL-17, or IL-12/23 inhibitors; should biologic failure occur, next treatment steps can include treatments with other methods of action, including JAK inhibitors (JAKi) or apremilast for patients with mild disease where biologics and JAKi treatments were inappropriate.[46] Patients can be switched to alternative treatments if necessary, and cautious treatment tapering should be considered for patients showing sustained remission.[46]

The heterogeneous nature of PsA encompasses several disease domains depending on the type of disease activity.[45]

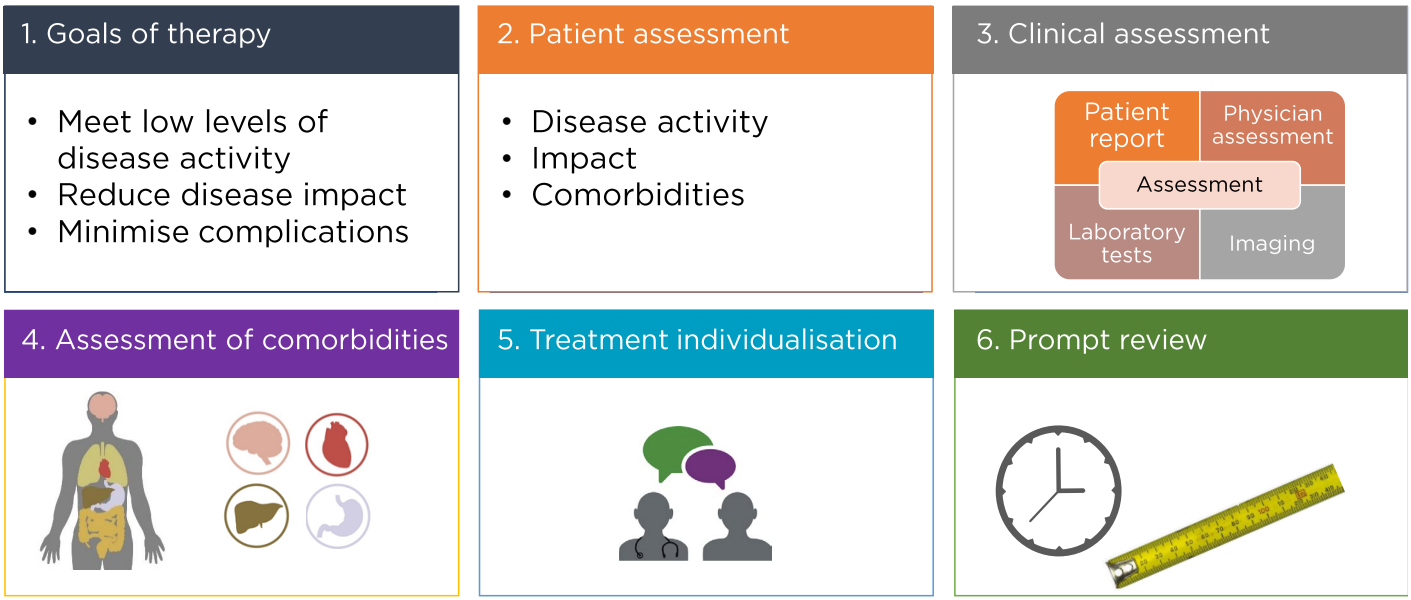

Figure 3: Overarching principles for psoriatic arthritis management.

Adapted from Coates et al.[45]

Patients with PsA often present with multiple domain involvement,[47] requiring periodic re-evaluation and therapy modification during the management process.[45] Previous research has also shown that patients who show the longest period of consecutive ACR20 and PASI 75 responses had the highest improvements in QoL measures such as EuroQoL-5 Dimensions Visual Analogue Scale (EQ-5D VAS) and Short Form (SF)-36 scores.[48]

Making the optimal treatment decision may be challenging because of the wide range of available therapies and limited head-to-head comparison data for patients with PsA. Data regarding currently available treatments, including IL-12/23, TNF, IL-17, phosphodiesterase 4, and JAKi show that all of these treatments have benefits for patients with PsA; between 40% and 70% of patients achieve ACR20 responses, and, more variably, 10% and 80% of patients achieve PASI 75 responses during treatment.[39,49-53] However, studies also show that patients with axial SpA did not respond equally across treatments. For example, patients with ankylosing spondylitis receiving ustekinumab, risankizumab, and apremilast did not show any significant improvements in Assessment of SpondyloArthritis International Society (ASAS) scores, compared with placebo; however, ASAS improvements were achieved in patients receiving adalimumab or secukinumab.[54-58] In the DISCOVER-1 and -2 trials, treatment with either dose of guselkumab resulted in improvement of axial symptoms, including Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores and spinal pain, compared with placebo ($p<0.001$), during 24 weeks of treatment in patients with active PsA and imaging-confirmed sacroiliitis.[59]

Diagnostic delays of 6 months or more can have a substantial impact on symptom severity in patients with PsA, resulting in increases in erosive disease, joint deformity, arthritis mutilans, sacroiliitis, functional disability, and chances of drug-free remission.[60] Studies have shown that treating-to-target, with tight disease control via regular evaluations and therapy adjustments as necessary to achieve minimal disease activity (MDA), results in improved arthritis, psoriasis, and function for patients with PsA.[61] Furthermore, the 2017 treat-to-target recommendations for patients with active SpA state that targets should include clinical remission and/or inactive disease of musculoskeletal and extra-articular manifestations, and that low or MDA may be an alternative target. Manifestations should also be used to define the treatment target and guide treatment decisions,[62] though different remission and MDA targets may differ slightly in terms of residual disease.[63]

Dr Coates concluded by underscoring the importance of considering the joints, entheses, and skin when making individualised treatment plans for patients with PsA, using the simplest measures for each assessment, and using MDA or a similar endpoint as the treat-to-target goal.

Panel Discussion

The faculty responded to a variety of questions during the panel discussion. The first question focussed on the longevity of responses seen with IL-23 inhibitors, and how this applies to clinical practice. Prof Reich responded that patients participating in clinical trials have usually had psoriasis for 15 years, demonstrating the need to identify patients who might benefit from early treatment course. He also noted the need for aggressive treatment for 2 years at the onset of disease to prevent the development of chronic disease.

The online participants asked Dr Coates about the possible differences between IL-23 and IL-17 inhibitors in the treatment of axial disease. She replied that more studies should be performed to differentiate axial SpA from PsA, noting that a large project is currently planned with the ASAS and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) to improve classification criteria that can be used in future studies. Imaging studies to accurately identify and classify differences between spinal and peripheral skeletal responses are also required. When asked if skin response would be predictive of entheseal disease response in patients with PsA, Prof Schett responded that the initial data with guselkumab show that it is effective in entheseal disease resolution, similar to PASI results seen with patients with psoriasis. However, he stressed that guselkumab studies focus on a specific subgroup of patients, and that patients with increased entheseal involvement, for example, may also benefit from treatment.

He noted that further studies are necessary to examine the effects of IL-23p19 inhibitors on other types of PsA.

Participants were also curious about the rapid speed of onset of IL-23 inhibitors. Prof Reich pointed out that, while IL-17 inhibitors show a fast onset of action, treatment with IL-23 inhibitors resulted in sustainable, long-term responses in patients with psoriasis. The results of the IXORA-R study show that ixekizumab results in greater changes in early treatment, compared with guselkumab,[64] though speed of response is usually not the main driver of treatment choice for most of his patients. Usually, a small subset (10–15%) of patients would prefer a treatment with a rapid onset of action and would benefit from treatment with an IL-17 inhibitor. However, the majority of patients in Prof Reich's practice, who have already had the disease for years, would prefer a treatment with sustainable, long-term responses, and would therefore benefit from treatment with an IL-23 inhibitor.

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In Darwin's Footsteps: Adaptation Through Innovation in Rheumatoid Arthritis

This scientific symposium took place twice on June 4th and 5th 2020, as part of the European League Against Rheumatism (EULAR) E-CONGRESS 2020

Chairperson: Georg Schett[1]

Speakers: Georg Schett,[1] Ronald van Vollenhoven,[2] Kunihiro Yamaoka,[3] Maya Buch[4]

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Meeting Summary

Prof Schett opened the session by explaining the overall theme and objectives of the symposium. Charles Darwin famously visited the Galápagos islands in 1835. His observations and collections of species of birds, also known as Darwin's finches, showed the small physiology variations in the birds. Each bird species had a different food habit and lifestyle that led to the evolution and adaptation of different beak shapes and sizes.

These facts contributed to the development of Darwin's theory of evolution by natural selection presented in his book "The Origin of Species by Means of Natural Selection." These findings played a pivotal role in the formation of his scientific theories on evolution and natural selection. Similarly, the management of rheumatoid arthritis (RA) has followed in Darwin's footsteps by evolving and becoming more complex, compelling innovative and collaborative solutions. The theory of evolution is not confined to animals and humans, but also provides a fundamental process in understanding diseases and there are several evolutionary chapters in RA. Research has advanced our ever-evolving and rapidly increasing understanding of RA pathology and molecular targeting which is flanked by a substantial and sustained development of new therapies leading doctors and patients to now have an expanding range of treatment options. This along with the progress in multidisciplinary treatment approaches; patients wanting to be actively involved in treatment decision making; the revolution of patient-centred digital communication using innovative, supportive technology; and the support of patient groups has led to the improved management of symptoms and better quality of life for patients with RA.

"In the long history of humankind (and animal kind, too) those who learned to collaborate and improvise most effectively have prevailed." (Charles Darwin 1809–1882)[1]

How Rheumatoid Arthritis Therapy Has Evolved: From Humble Beginnings to Effective, Targeted Treatments

Professor Ronald van Vollenhoven

Prof van Vollenhoven discussed the evolution of therapy over the last 20–30 years, as well as the current and emerging paradigms of care for patients with RA. Firstly, RA clinicians have learned that the disease can be modified and not just treated symptomatically. This discovery has profoundly changed the disease. In addition, the development of highly precise tools has enabled reliable clinical assessment to ascertain the degree of inflammation, disease activity, radiological damage, and the impact on patient's lives.

The understanding of the pathophysiological, inflammatory, and destructive processes at the molecular and cellular levels involved in RA has led to the development of multiple therapeutic options, including conventional, biological, and small-molecule JAK inhibitors.[2-20]

Over the past 70 years, treatment for RA has changed profoundly, evolving from a strategy of providing only symptomatic relief, to the realisation of regimens that impact disease activity and slowing or halting structural joint damage. Drug therapy for RA has evolved with improving efficacy and the impact on disease activity and radiographic progression, from gold

salts in the 1930s to biologic response modifiers (biologic disease-modifying antirheumatic drugs [bDMARD]) (e.g., TNFα inhibitors, IL-1 inhibitors, B-cell inhibitors, T-cell costimulation inhibitors, and IL-6 receptor inhibitors) and finally to targeted synthetic DMARD approved in the last decade.[7-20] When reviewing clinical trials with these different agents, it is important to realise that there have been both great successes and some failures (anti-CD4 inhibitors and spleen tyrosine kinase [SYK] inhibitors).[21]

The exponential development and availability of these improved therapeutic options, with different efficacy and safety profiles, were results of research and improved understanding of the RA pathology and disease.[2-5,7,21] This, in turn, has changed the treatment paradigm facilitating consideration of patient choices, opinions, fears, and expectations, thereby compelling a more patient-centred treatment approach and[22,23] enabling personalised treatment for patients with RA.

In addition to new drugs to treat RA, novel and reliable measurements have been developed to assess the outcomes of therapeutic intervention and have been incorporated into treat-to-target (T2T) approaches for managing RA. The tools for measuring disease activity have allowed us to reconsider the goals of treating our patients. Patients with active RA desire decreased pain and improved mobility and function. This translates into a need to control the inflammation with an overall goal of achieving a state of remission and sustained remission in those who can potentially achieve this. Low disease activity and sustained low disease activity is an alternative goal in those unable to achieve remission, particularly in long-standing disease.[6,23,24]

Two decades ago, Kirwan[25] demonstrated that the initial correlation between inflammation and disability (e.g., pain and stiffness) is high and fluctuates with time (potentially attributable to the natural course of the disease or therapeutic interventions). As the disease progresses, radiographic damage develops and increases in correlation with disability and joint destruction, which becomes more relevant to the degree of disability experienced later in the disease process. Therefore, current treatment strategies target reducing inflammation and preventing, or limiting, radiographic damage to achieve optimal functional status with the least amount of disability for patients with RA. This involves early intervention with a proposed 'window of opportunity' varying from 3–6 months to the first 2 years.[26,27]

One of the most recent therapeutic developments for RA has been the development of JAK inhibitors. Studies comparing JAK inhibitors with anti-TNF agents have shown to be statistically significant superior or noninferior.[28-30] For both patients and clinicians, it is exciting to have a class of agents available with this level of efficacy.

The significant evolution in understanding the underlying pathophysiological mechanism and development of new treatment modalities in RA has ultimately led to the need for early diagnosis, initiation of intensive therapy, and 'tight control' monitoring driven by regular measurements of disease activity. To achieve successful monitoring of the RA patient, there are two aspects requiring consideration. The first is to scientifically and objectively assess the degree of disease activity using instruments such as the Disease Activity Score 28 (DAS28), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI). These can be used along with the American College of Rheumatology–European League Against Rheumatism (ACR–EULAR) remission definition to monitor the patient's remission status.[31] Secondly, the patient's health, quality of life, and functional status may be ascertained using one of the patient-reported outcomes such as the Health Assessment Questionnaire (HAQ), Routine Assessment of Patient Index Data 3 (RAPID3), Rheumatoid Arthritis Disease Activity Index (RADAI), Rapid Assessment of Disease Activity in Rheumatology (RADAR), or the Short Form 36 Health Survey (SF-36).[32-34] It is important to balance the clinician's goals of treatment with those of the patient by integrating current treatment strategies with a patient-centred approach. This involves seeing the patient as a unique individual and approaching the patient from a biopsychological perspective. These need to be viewed in the context of the environment of the patient (friends, family, and social support structure), their emotional wellbeing, and relationships.[35,36] It is this approach to patient care that we must strive for if we are to meet the challenge posed by William Osler (1849–1919) over a century ago that: "The good physician treats the disease; the great physician treats the patient who has the disease."[37]

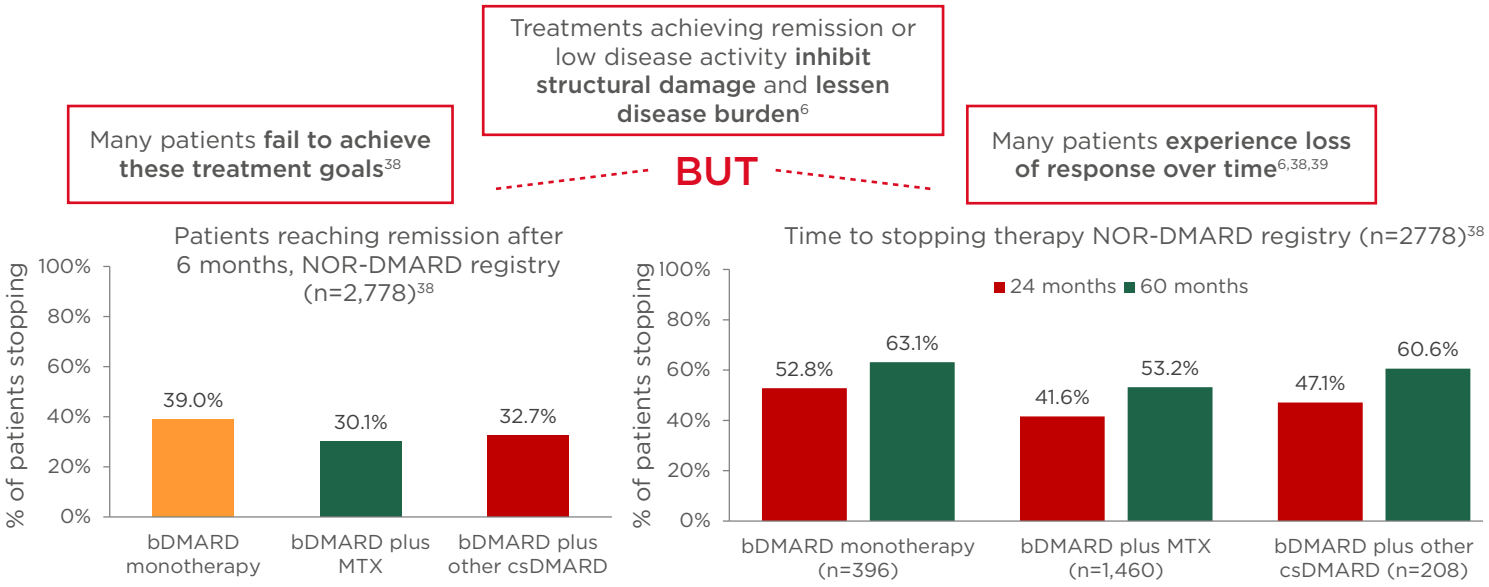

Figure 1: Many patients with rheumatoid arthritis fail to achieve treatment goals or experience loss of response over time.

Real-world data from the Norwegian DMARD (NOR-DMARD) registry analysing 2,778 treatment courses, including 396 biologic disease-modifying antirheumatic drug (bDMARD) monotherapies, 1,460 bDMARD plus methotrexate, and 208 bDMARD plus other conventional synthetic DMARD. There was no significant difference in efficacy between the bDMARD groups and the most common reasons for stopping bDMARD therapy were lack of efficacy, followed by adverse events.

bDMARD: biologic disease-modifying antirheumatic drug; csDMARD: conventional synthetic DMARD; MTX: methotrexate.

Adapted from Olsen et al.[38]

"The good physician treats the disease; the great physician treats the patient who has the disease" - William Osler, 1849–1919

Indeed, many patients still do not reach the therapeutic targets, and many experience loss of response over time, despite innovative therapeutic strategies and assessment tools.[6,38,39] In fact, real-world data from the Norwegian DMARD (NOR-DMARD) registry with 2,778 patients (Figure 1)[38] found that less than 50% of patients achieved a strict definition of remission (DAS28-4; erythrocyte sedimentation rate <2.6) after 6 months of bDMARD monotherapy or combination therapy. In addition, almost 50% of patients stopped therapy after 24 or 60 months. Lack of efficacy was the most common reason for stopping treatment across all treatment groups. This was followed by adverse events.[38] These data are further supported by other studies demonstrating that up to 50% of patients starting a new DMARD must stop it within 12–18 months,[6] and in those who do achieve initial symptom control, only a few (11%) maintain sustained clinical remission by 5 years.[40] One of the future goals of the rheumatology community is to achieve bDMARD-free remission, i.e., to start the patient on an advanced therapy to achieve disease control and then stop therapy as a result of sustained remission.

This is not easy to accomplish and it remains an enigmatic goal, as shown by Huizinga et al.[41] who found that most patients (84%) who discontinued an advanced therapy had a subsequent flare of disease activity.

In the evolution of patient care in RA, there remain limitations requiring improvement. Even though many RA patients may not achieve the set therapeutic goals, they do not switch to alternative treatments because of concerns over toxicity of other treatments and accepting the status quo.[38] Important symptoms, such as pain, physical function, and fatigue are

not adequately assessed and addressed.[42] Monotherapy as a general rule is less effective than combination therapy, with higher rates of stopping therapy with bDMARD monotherapy than with bDMARD combination therapy.[38] Even with current T2T strategies a significant percentage of patients continue to have moderate to high disease activity.[6,43] There is still a need for future therapies to enhance already established efficacy of current therapeutics and in patients who remain unresponsive to current treatments.[6,31,43]

In the future, we must adapt and learn to explore all the options and possibilities, including information technology and bioinformatics. Evolving technologies could enable extensive recording of real-time disease characteristics and molecular processes in individual patients to generate personal big data. Rheumatologists will require new strategies for the management of their patients to develop data-driven individualised concepts resulting in better diagnosis and treatment. These datasets could include devices to store data; genome typing to identify disease-associated genes; noninvasive imaging to assess inflammation; gene expression analysis to discriminate between states of viral, bacterial, or other inflammation; and proteomics and autoantibody analysis.[44] These evolving, sophisticated, and rapid techniques provide us with optimism and excitement about positive future developments.

In summary, even though the field of rheumatology has evolved extensively over the years, there is still more we can do for our patients. We want to achieve remission for all patients, which means that we may have to treat them earlier. The management of patients with RA is a fluid and evolving concept that has developed over time. In the near future, and also in the longer term, we can anticipate exciting developments in our ability to help patients living with RA. This will in part be based on our evolving understanding of RA pathology and the integration of new identification and validation techniques, resulting in novel therapeutics. As a result of this more in-depth understanding and range of therapies, RA management strategies can become more patient-centred and individualised.

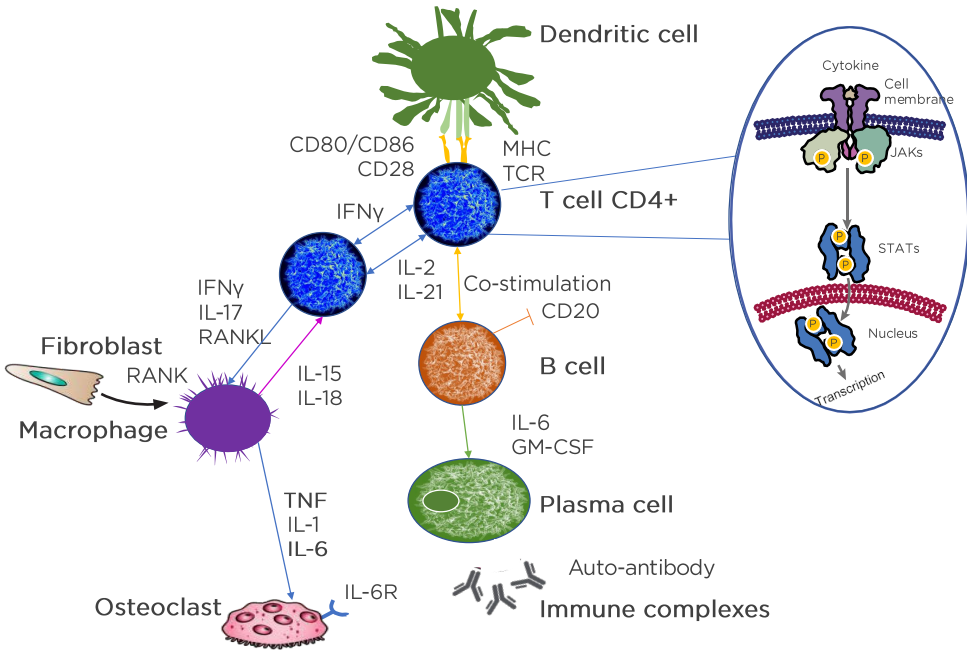

Figure 2: The understanding of pathological pathways has led to an array of treatment options.

Identification of molecular targets requires clear understanding of complex cytokine pathways.

APC: antigen presenting cells; CD: cluster of differentiation; GM-CSF: granulocyte-macrophage colony-stimulating factor; IL-6R: IL-6 receptor; MHC: major histocompatibility complex; RANKL: receptor activator of nuclear factor-κB ligand; TCR: T-cell receptor; P: phosphorylation.

Adapted from Smolen et al.[3] and Virtanen et al.[47]

Whilst RA management is continually evolving, many challenges such as low patient adherence, lack of effective treatment switching, and high disease activity despite individualised T2T strategies still exist.

Evolution of Molecular Targeting

Professor Kunihiro Yamaoka

Modern advances in medical treatment have greatly benefited patients living with RA. The development of even more effective targeted therapies could be compelled by further discovery of the disease's molecular pathology.[7,45-47]

Looking into the histology of RA, some details are known about what is happening in the synovial fluid. RA is a complex disease that involves interactions between a variety of immune modulators and signalling pathways. The immune response consists of a series of communications between many cell types. Interactions between antigen-presenting cells (APC) and T cells may initiate and amplify T-cell-dependent immune responses. Immune modulators, such as cytokines, and cells of the immune system, including neutrophils, macrophages, T cells, B cells, plasma cells, and autoantibodies, all contribute to the pathophysiology of the disease, and ultimately, are responsible for the joint damage in RA.

The synovial tissue in patients with RA is enriched with mature APC and many T lymphocytes. Dendritic APC present antigens to T cells for activation, and activated T cells then activate B cells, which then differentiate into plasma cells or memory B cells. Cytokine production by APC and T cells includes receptor activation of NF-κB ligand (RANKL), IFNγ, TNFα, IL-2, IL-6, and IL-17. T cells can express NF-κB ligand which can differentiate precursor cells into bone-resorbing osteoclasts, which can lead to bone loss and disruption in the joints.[3,48]

In each cell affected by cytokines, the triggered cytokine signalling cascade runs in the cytoplasm and one of these is JAK. JAK is activated directly after the cytokine binds to its receptor and JAK activates signal transducer and activator of transcription (STAT), which, upon dimerisation, move into the nucleus and regulate the transcription of multiple genes (Figure 2).[47]

With this immune response cascade, the JAK–STAT pathway is heavily involved in RA. This has led to the advent of the JAK inhibitors, which are quite different to the bDMARD drugs because these molecules are able to enter the cytoplasm to inhibit the activation of JAK.[47] Individual cytokines interact with specific intracellular pathways. Other intracellular signalling pathways involved in RA include the MAPK, SYK, NF-κB, and P13K.[48] The MAPK pathway has been extensively studied; however, a p38MAPK inhibitor has proven unsuccessful as a RA treatment option when compared to methotrexate.[49] Theories for this include dose limitations as a result of toxicity, altered biodistribution of newer molecules preventing central nervous system penetration, incorrect isoform targeting, blocking downstream of the signalling pathway will not block upstream kinases, and kinases in the MAPK pathway (e.g., p38α) may have a regulatory role in the induction of anti-inflammatory cytokines.[49,50] Similarly, SYK inhibitors have also had limited success as an RA treatment. Although blocking SYK with fostamatinib and MK-8457 did not demonstrate statistically significant ACR 20% improvement criteria scores versus placebo, there was a signal of improvement on osteitis, synovitis, and erosion, highlighting the need for upstream blockade of cytokine pathways.[50-52]

The JAK–STAT pathway has a key role in transmitting signals to the nucleus and inducing production of more cytokines and other factors.[53] Excessive cytokine signalling via the JAK–STAT pathway leads to inflammation, autoimmunity, bone erosion, and cartilage damage, which are intrinsic to RA pathology.[54-60] There are four members of the JAK family: JAK1, JAK2, JAK3, and tyrosine-protein kinase 2 (TYK2). Different individual cytokines signal through different pairs of JAK family members, and by activating diverse STAT pairs, they can selectively mediate a wide array of downstream signalling. These molecules sit docked on the intracellular tails of the receptor molecules embedded in the membranes of the cell, and they will pair up with either one of their own kind (homodimers) or with other members (heterodimers). JAK1, JAK2, and TYK2 are involved in signals by several cytokine targets in inflammatory conditions, including IL-6, IL-12, IL-23, granulocyte macrophage colony-stimulating factor, and IFN. Specific JAK and STAT pairs mediate the message propagated

by different cytokine signals. Specific pairing of JAK determines the signal transmitted to the nucleus, and the output produced, namely, JAK3 in conjunction with JAK1 is an important component of signal transduction for cytokine receptors that utilise the common gamma chain such as IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21; JAK2 plus JAK1 plus TYK2: IL-6, IL-11, IL-13, IL-27, IL-31, IL-35; JAK2 plus JAK2: granulocyte-macrophage colony-stimulating factor, erythropoietin, thyroid peroxidase; JAK1 plus TYK2: IFNα, IFNβ, IL-10, IL-20, IL-22, IL-28; and JAK2 plus JAK1: IFNγ.[53]

Proteins including JAK and STAT require phosphate groups for activation. A common source of this phosphate is ATP, which transfers chemical energy within cells. JAK are phosphotransferases that catalyse the transfer of phosphate from ATP to various substrates. The transfer of a phosphate group from ATP to a JAK activates the JAK. Activated JAK pairs facilitate the phosphorylation of STAT. JAK inhibitors competitively inhibit ATP binding because of their ATP-like structure by reversibly binding to ATP-binding sites. Without phosphorylation, JAK proteins remain inactive and are unable to phosphorylate their relevant STAT proteins. STAT proteins are therefore unable to dimerise and translocate to the nucleus and the expression of physiological modulators are inhibited.[47,61] Because JAK are key regulators of several cytokines that have been implicated in RA development and progression, they have been identified as potential targets for inflammatory diseases.[50,53]

Even though we have an array of available therapeutic options, there is still room for improvement in patient satisfaction rates in the treatment of RA. Several patient surveys have shown 32–77% satisfaction rates with current treatments and care.[62-65] This highlights a need for further treatment options. Furthering our understanding of RA pathology can assist in improving treatment options and management. There remains a need to support researchers in identifying new targets in preclinical research, provide explanations to physicians for drug efficacy and safety outcomes seen in clinical practice, and provide patients with knowledge of RA disease to enable patient inclusion in treatment decisions. A longitudinal monitoring analysis of drug response at multiomics levels in the peripheral blood of patients with RA revealed that drug treatments alter the molecular profile closer to that of healthy controls at the transcriptome, serum proteome, and immunophenotype level.[66] This study highlighted that is not simple to identify which patients would benefit most from specific treatments.

We need to expand our knowledge of RA pathology to further guide therapy choice and management by outlining which patient groups would benefit from therapies against each specific molecular target, thereby, enabling more personalised therapeutic strategies.

In summary, the identification of molecular targets requires a clear understanding of complex cytokine pathways. RA pathology is an elaborate and complex network of signalling and molecular pathways. Despite differences in the mechanism of action, current DMARD have similar response rates and there is an unmet need for improving treatment options for patients with RA. Recent advances in technology and management strategies have allowed for further understanding of RA disease. A better understanding of RA pathophysiology can lead to the discovery of new or improved therapies, e.g., JAK inhibitors, though further study is required to understand treatment safety and efficacy and identify which individual patients may benefit from which drug. This information is key to the evolution of a patient-centric approach in RA management to ensure that we can address the quality of life of the patient.

Evolving Trends in Treatment Decision Making

Professor Maya Buch

Outcomes in patients with RA have dramatically improved over the past two decades as a result of combined efforts of better disease activity assessment and diagnostic tools along with a better armamentarium of therapeutic options.[2,3] This has allowed us to focus on a T2T strategy with a patient-centric approach.[6] Achieving patient-centred care across the spectrum of therapy choices has also evolved over time. Historically, the most common consultation with our patients was a paternalistic decision-making model where the patient passively agrees with

healthcare professional (HCP) recommendations. More recently, the informed decision-making model of enabling patient empowerment and autonomy, with the HCP providing information and the patient making informed decisions, and the shared decision-making model, where the patient and HCP share equal involvement with both parties having an active dialogue to express preferences underpinned by clinical expertise to reach a consensus on the agreed management route, have been developed.[22] This notion has been advocated by various professional and organisational guidelines and recommendations, including the EULAR 2019 RA management recommendations.[6]

"Patients require access to multiple drugs with different modes of action to address the heterogeneity of RA; they may require multiple successive therapies throughout life."

"Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist."

"Patient education may increase adherence to medication... patient education forms the implicit and inseparable basis for shared decision-making."

Personalised care requires both the selection of a tailored therapy integrated with the involvement of the patient in the decision-making process to ensure the best possible outcomes. Identifying real-life factors that drive treatment choice is essential to optimal patient care. The physician considerations include overall drug efficacy; targeting remission; rapid drug onset and initial response, convincing efficacy evidence-based, clinical trial data; and comorbidities and drug safety intersection.[67] The patient considerations include the long-term drug use associated with 'reliance' and 'dependence', the occurrence of side effects, perception of alternative treatment options, and the psychosocial aspect of the emotional impact/psychological burden of removing/starting medication with the stigma of requiring long-term disease modification.[68] Patients also have preferences for the mode of administration of drugs and these preferences will affect treatment decisions. The clinical factors remain centrally crucial in defining which drugs may be important, and the route of administration is important when tailoring to the individual patient. Oral agents are perceived as better, providing autonomy and independence and rapid onset of action; however, some patients are reassured by intravenous/parenteral preparations which provide the comfort/safety of the hospital environment and reassurance from HCP. Whereas subcutaneous injections could provide patients with the confidence of a drug.[69,70] These psychological aspects and perspectives of a patient are important to convey and listen to when we engage within our consultation.

A survey found that a large proportion understands the benefit of goal setting in clinical practice showing alignment to the physician-driven T2T strategy. The survey also highlighted that physicians may not articulate the goals of the T2T strategy when consulting with patients and almost three-quarters of the patients suggested that the HCP had not discussed an approach that achieves goals.[36] Therefore, it is very important to verbally articulate our thoughts to the patient.

From a physician's perspective, there are several composite indices to assess the disease activity of RA. The DAS28 being one of the most well established, but also the SDAI, CDAI, and more recently the Boolean remission criteria. The overall cut-off values of these assessments are used as an indicator of treatment efficacy in a patient; however, it is important to understand what components drive these different composite indices. The DAS28 score is a complex formula of the tender joint count 28, swollen joint count 28, erythrocyte sedimentation rate or C-reactive protein value, and the Patient Global Assessment (PGA).[31] The composite score transforms and weighs the component variables, resulting in a stronger influence of tender rather than swollen joints and a very high contribution of acute-phase reactant levels to the score, even within their normal ranges. Consequently, swollen joints can still be present during remission and drugs that interfere directly with acute phase reactant synthesis show exaggerated DAS28 rates. Conversely, patients may not achieve remission but have an absence of swollen joint counts.

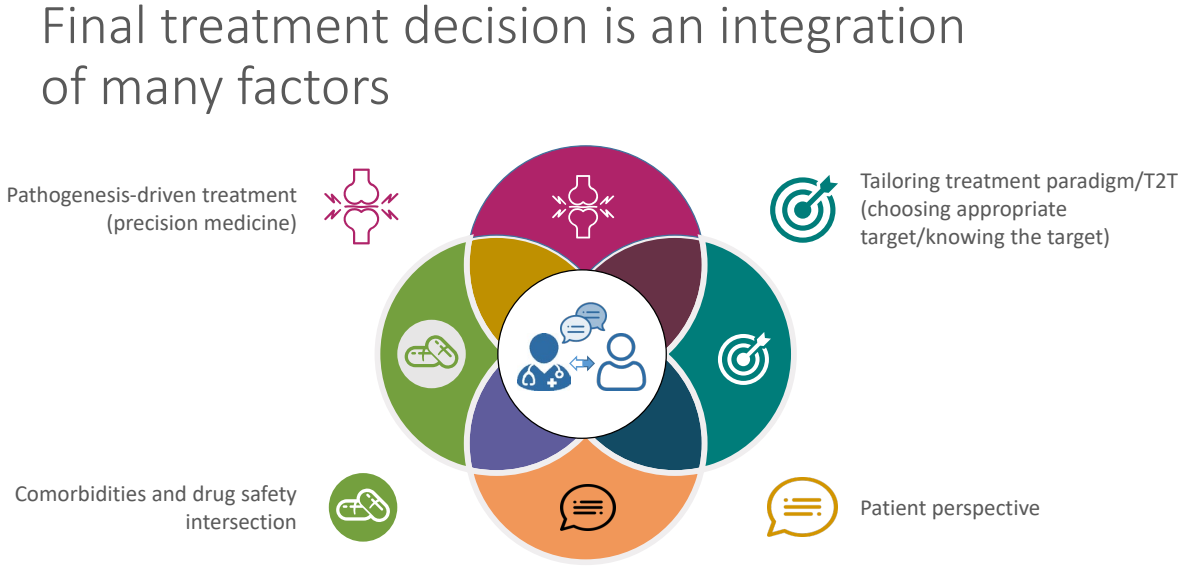

Figure 3: Rheumatoid arthritis treatment decisions requires integration of many factors.

T2T: treat-2-target.

Adapted from Smolen et al.[6]

It is important to realise the discrepancy between the total disease activity score and the components of what the patient is telling us.[3]

Data from the Vienna group (n=646 RA patients) reviewing the perceptions of RA disease activity, as quantified by the PGA and by the Evaluator's Global Assessment (EGA), demonstrated the most significant determinants for the cross-sectional and longitudinal discrepancy between the PGA and the EGA are pain (75.6%) and swollen joint count (60.9%), respectively. Highlighting the importance of recognising how pain that is not related to the inflammation also inputs into the disease activity assessment, which can be uncovered with improved engagements with our patients.[71] As the patient's clinical profile changes, the patient's expectations adapt, and the physician appraisal evolves. Therefore, the physician's perception of risk–benefit profiling and appropriate treatment choices evolve over time.[68]

With the advent of targeted therapies, initially with biologics and more recently with the oral synthetically targeted ones, there has been a tremendous emphasis and utility of registry data to inform the safety aspects of these drugs. These have been of enormous value and there may be some equivalency with certain kinds of toxicity (there are differences in the safety profiles of treatment options).[72] The safety profiles of drugs become more pertinent in the context of the comorbidities in RA which are associated with poorer outcomes in patients. Most patients with RA are affected by a number of associated comorbidities.

Comorbidities in RA are associated with increased morbidity and mortality, impaired quality of life and treatment response, and increased complexity of management and its costs.[73,74] Because these comorbidities can change over time, the scenarios are constantly evolving. To successfully manage RA, comorbidities should be carefully considered and treated in addition to prescribing medications. Comorbid conditions may impact treatment regimens of RA, or the prescribed drugs may worsen the comorbidity. Physicians may also be forced to prescribe RA medications that exacerbate the comorbid conditions.[75]

What becomes evident to us is that integrated management of comorbidities in RA is needed to determine the best treatment option for each patient managed through a rheumatologist-led multidisciplinary approach.[6,76] It is also

increasingly recognised that the concordance between the patient and HCP can improve outcome through adherence. Adherence to medication in patients with RA is low, varying between 30 and 80%. Risk factors for the lack of adherence include comorbidities, complex regimens, poor patient–HCP relationship, perceived treatment benefit, and lack of patient knowledge. Patient/HCP conversations to improve adherence and outcomes should cover the diagnosis and prognosis of illness, the need for proposed therapy, risks and benefits associated with treatment, the patient's personal beliefs, concerns about prescribed medication, and concerns for the course of therapy.[77]

The level of desire for involvement in treatment decision is unique to each patient and physicians should not assume that all patients desire an equal partnership in treatment involvement. Results from a study interviewing patients living with RA for more than a decade (n=20) showed that the majority of patients (75%) followed a shared decision model; however, the level of involvement varied within this group ranging from equal involvement from both sides to a more paternalistic decision model.[22] Clinical expertise has to inform and underpin the patient and their education. It is important to know our patients and recognise which is their preferred approach to formulate the best treatment decision with them.

Whilst the holy grail of RA treatment may be biomarker- and pathogenesis-driven, when it comes to clinical implementation in our practice, the final treatment decision requires an integration of a multitude of factors (Figure 3).[6] These factors include the pathogenesis-driven treatment (precision medicine), tailoring treatment paradigm/T2T (choosing appropriate target/knowing the target), patient perspective, and the comorbidities and drug safety intersection.[6] It is only when we bring these factors together in an active dialogue with our patients that we achieve an optimal outcome.

In summary, the final treatment decision is an integration of many factors aiming to deliver optimal treatment outcomes. The contemporary management of patients with RA thus focusses on an integrated patient-inclusive approach. Improving communication barriers for patient information and education can promote the patient-centred integrated management approach of RA.

CONCLUSION

Over the last two decades, significant progress has been made in understanding the underlying pathophysiological mechanisms and treatment modalities in RA. These aspects have ultimately led to the unassailable need for early diagnosis, initiation of intensive T2T therapy, and tight control monitoring driven by regular measurements of disease activity. A combination of these aspects with a shared decision-making model, with an active dialogue to express preferences underpinned by clinical expertise to reach a consensus on the agreed management route, can result in significantly improved outcomes in RA patients.

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Latest Highlights on Biologic Treatments for Psoriatic Arthritis from EULAR 2020

These posters and oral presentations were presented from 3rd to 6th June 2020 at the European League Against Rheumatism (EULAR) E-CONGRESS 2020

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Summary

Psoriatic arthritis (PsA) is a chronic, heterogeneous, immune-mediated arthritis characterised by joint inflammation and diverse clinical manifestations including psoriasis, peripheral and/or axial joint disease, enthesitis, and dactylitis. In recent years, several effective biologic treatments for PsA, including TNF inhibitors, IL-12/23 inhibitors, and IL-17 inhibitors, have been introduced. Several ongoing studies are examining the potential efficacy and safety of PsA treatments, including the monoclonal antibodies guselkumab, which specifically binds to the p19-subunit of IL-23, and ustekinumab, which binds to IL-12/23. The results of the Phase III DISCOVER-1 and -2 trials with guselkumab and the

PsABIO trials with ustekinumab show that these treatments result in sustained improvements in skin, joint, and soft-tissue manifestations of PsA, with no new safety signals, in adult patients with active PsA.

Summary of the DISCOVER-1 and -2 Trial Designs

The DISCOVER-1 trial was a Phase III, randomised, double-blind, placebo-controlled study that aimed to examine the efficacy of guselkumab 100 mg, given subcutaneously every 4 or 8 weeks (q4w or q8w, respectively) on PsA outcomes, including joint and skin symptoms, physical function, and quality of life, through 52 weeks of treatment.[1] The study included adults with active PsA (at least three swollen and three tender joints; C-reactive protein: ≥0.3 mg/dL) who had not responded to earlier treatment; approximately 30% of patients had received up to two TNFα inhibitor (TNFi) agents. A total of 381 patients were randomised 1:1:1 to guselkumab 100 mg q4w; guselkumab 100 mg at Week 0 and Week 4, and then q8w; or placebo. Placebo patients crossed over to guselkumab q4w at Week 24.[2] The DISCOVER-2 trial design was similar to that of DISCOVER-1,[3] and examined treatment efficacy and safety through Week 52, but in 739 patients with active PsA who were biologic-naïve.[4]

The Efficacy and Safety of Guselkumab, an Anti-IL-23p19 Monoclonal Antibody, in Patients with Active Psoriatic Arthritis

Doctor Christopher Ritchlin, Professor Iain B. McInnes, and Professor Philip Helliwell

In the DISCOVER-1 trial, patients receiving guselkumab 100 mg q4w and q8w showed improved American College of Rheumatology (ACR) 20% improvement criteria (ACR20) response rates, which were maintained at Week 52 in 73.4% (q4w) and 59.8% (q8w) of patients. Similar response patterns were also seen for the more rigorous ACR50 and 70 criteria.[2] Response rates were comparable in patients who had received prior TNFi treatment, and in patients who crossed over to guselkumab treatment at Week 24. Treatment with both doses of guselkumab maintained improvements in joint and skin symptoms, dactylitis, enthesitis, and quality of life components through 52 weeks in patients with active PsA who were biologic-naïve or had previous TNFi experience. Treatment was safe and well tolerated, and consistent with previous studies regarding guselkumab safety in psoriasis.[5]

In the DISCOVER-2 trial, outcome measurements included ACR response rates and a PsA-modified van der Heijde–Sharp (vdH-S) score measuring joint damage progression. ACR20 response rates at Week 52 were 70.6% (q4w) and 74.6% (q8w), with similar response patterns for the ACR50 and 70 criteria. Changes in vdH-S scores in Weeks 0–24 (0.62) and Weeks 24–52 (0.46) were comparable in patients receiving the q4w dose; less radiographic progression occurred in Weeks 24–52, compared with Weeks 0–24, for patients receiving the q8w dose (0.23 versus 0.73) and for patients receiving the q4w dose compared with placebo (1.00 versus 0.25). Guselkumab treatment resulted in prolonged improvements in joint and skin symptoms, as well as inhibition of radiographic progression, through Week 52.[4]

A study examining the efficacy and safety of guselkumab in patients with PsA with imaging-confirmed axial involvement consistent with sacroiliitis in the DISCOVER-1 and -2 trials, found that treatment was associated with a reduction of axial symptoms after 24 weeks of treatment. Both guselkumab doses resulted in significant differences in mean least squares changes from baseline to Week 24 in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores (-2.67 [q8w] and -2.68 [q4w] versus -1.35 [placebo]; $p<0.001$) and spinal pain (-2.73

[q8w] and -2.48 [q4w] versus -1.30 [placebo]; p<0.001). A significantly greater proportion of guselkumab-treated patients also achieved BASDAI 50 responses (40.5% [q8w] and 37.9% [q4w]), compared with placebo (19.1%; p<0.01 for both doses) at Week 24.[6]

A network meta-analysis of 26 Phase III studies comparing guselkumab treatment with other targeted therapies for PsA showed that guselkumab treatment is comparable to most treatments regarding improvements in arthritis, soft-tissue damage, physical function, and safety outcomes. For the ACR20 response, the q4w and q8w guselkumab doses ranked fifth and eighth, respectively, out of 20 interventions, and were comparable to IL-17A inhibitors and most TNFi agents, with similar findings for ACR50 and 70 responses. For Psoriasis Area Severity Index (PASI) 90 responses, both guselkumab doses ranked first and second out of 15 interventions and were highly likely to provide a greater benefit for patients, compared with most other agents. Findings for the PASI 75 and 100 responses were similar to those of PASI 90. Both guselkumab doses ranked in the top five out of 19 interventions regarding adverse events and severe adverse events, comparable to IL-17A inhibitors and TNFi agents.[7]

Summary of the PsABIO Study Design

The PsABIO study evaluated the effectiveness, tolerability, and persistence of first-, second-, or third-line treatment with ustekinumab or TNFi in PsA, and included outcome data for patients achieving minimal disease activity (MDA) or very low disease activity (VLDA), as well as clinical Disease Activity in PSoriatic Arthritis (cDAPSA) low disease activity and remission.[8-10] The 12-month follow-up study included 929 eligible patients, of whom 438 received ustekinumab and 455 received a TNFi.[10]

Efficacy and Persistence of Ustekinumab, an IL-12/23 Inhibitor, in Patients with Psoriatic Arthritis

Professor Josef F. Smolen, Professor Laure Gossec, and Mister Kirk Geale

The introduction of IL-12/23 inhibition with ustekinumab heralded the first new biologic mode of action after TNFi, though there is a current lack of real-world data comparing these therapies in patients with PsA. In the PsABIO cohort comparing ustekinumab with TNFi treatment effectiveness at 12-month follow-up, the observed data showed differences in the proportion of patients achieving MDA, VLDA, cDAPSA low disease activity, and remission in favour of TNFi. However, after propensity score (PS) adjustment for baseline differences, there were no significant differences in odds ratios between the groups for achieving these targets at 12 months. Comparisons of 6- and 12-month unadjusted data showed sustained MDA and VLDA responses with both ustekinumab (21.8%) and TNFi (29.5%) treatment, with similar proportions of patients achieving these targets between Months 6 and 12 (17.0% and 20.3%, respectively).[10]

A comparative analysis of 1-year persistence of ustekinumab and TNFi within the PsABIO cohort showed a promising persistence profile for ustekinumab. Treatment persistence (up to 15 months of follow-up) was defined as time between start of first biologic disease-modifying antirheumatic drug (bDMARD) treatment in PsABIO, stopping or switching to another bDMARD, or withdrawal from treatment. Persistence was compared using a Cox regression analysis, with PS adjustments for baseline imbalances in demographics and disease-related covariates. Concomitant methotrexate use and skin involvement (body surface area: <3%, 3–10%, and >10%) were added to the Cox model to observe their possible influence on the PS-adjusted treatment effect. The results showed that 121 out of 438 (28%) and 134 out of 455

(29%) patients who began ustekinumab and TNFi treatment, respectively, stopped or switched treatment prior to Month 15, with the probability of treatment persistence decreasing with each subsequent treatment line.[11]

No statistically significant differences between ustekinumab and TNFi persistence were seen in the PS-adjusted Cox analysis for stopping or switching treatment (ustekinumab versus TNFi) (hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.60–1.13). However, patients who were receiving bDMARD monotherapy (without methotrexate) and had widespread skin involvement (body surface area: >10%) showed improved drug persistence with ustekinumab, compared with TNFi (HR: 0.61; 95% CI: 0.42–0.90, and HR: 0.41; 95% CI: 0.19–0.89, respectively).[11]

Efficacy and Persistence of Ustekinumab in Sweden

Further evidence for ustekinumab's favourable treatment persistence profile comes from a population-based study in Sweden comparing time to discontinuation of a TNFi (adalimumab), an IL-17 inhibitor (secukinumab), and an IL-12/23 inhibitor (ustekinumab).[12] Data were collected from population-based health data from the Swedish National Patient Register, Swedish Prescribed Drug Register, and Swedish Cause of Death Registry. Discontinuation was defined as a treatment switch to any other PsA-indicated biologic, or failure to redispense treatment within a grace period following end of drug supply.

A total of 3,620 discontinuation events across 4,649 treatment exposures (adalimumab: 3,255; secukinumab: 887; ustekinumab: 507) were found in the main analysis. The results of the multivariate main analysis showed that patients receiving ustekinumab had significantly lower discontinuation rates, compared with adalimumab (HR: 0.56; 95% CI: 0.49–0.64). In the multivariate sensitivity analysis, both ustekinumab (HR: 0.81; 95% CI: 0.70–0.94) and secukinumab (HR: 0.82; 95% CI: 0.70–0.95) treatment resulted in significantly lower discontinuation rates, compared with adalimumab. Previous biologic experience also had a significant ($p<0.05$) impact on discontinuation risk. The results show that ustekinumab treatment results in an improved treatment persistency profile, compared with adalimumab.[12]

Conclusions

In the DISCOVER-1 and -2 trials, treatment with the IL-23p19 inhibitor guselkumab resulted in the improvements of several PsA-related joint and skin symptoms, dactylitis, enthesitis, and quality-of-life outcomes through 52 weeks, compared with placebo, in patients with active PsA, with no new safety signals. In patients with PsA and axial involvement, guselkumab was associated with a reduction in axial symptoms after 24 weeks of treatment. A comparative analysis of guselkumab showed that it ranks consistently equally with other PsA treatments in terms of PsA-related measurements, including improvements in arthritis, soft-tissue damage, physical function, and safety outcomes. Treatment with the IL-12/23 inhibitor ustekinumab resulted in comparable MDA, VLDA, and cDAPSA outcomes and favourable persistence profiles, compared with TNFi, in patients with PsA.

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Abstract Reviews

Herein we present a selection of abstract reviews from this year's EULAR congress, including a summary of the first international awareness day for paediatric rheumatic diseases.

Understanding Joint Replacement Surgery in Axial Spondyloarthropathy

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Ankylosing spondylitis, axial spondyloarthropathy (AxSpA), joint replacement, spondyloarthritis, spondyloarthropathy.

Citation: EMJ Rheumatol. 2020;7[1]:50-52. Abstract No: AR1.

BACKGROUND AND AIMS

Axial spondyloarthropathy (axSpA) is a form of inflammatory arthritis that primarily affects the axial skeleton and sacroiliac joints but can also be associated with peripheral arthritis. Rapid advances in the field of axSpA have led to faster detection, diagnosis, and treatment of this disease. This improved management has led to enhanced level of function and quality of life for patients; however, despite this, a proportion of patients are still requiring joint replacement surgery.

The Ankylosing Spondylitis Registry of Ireland (ASRI) is a source of epidemiological data on patients with axSpA in Ireland. Given the large size of the ASRI to date, it provides a prime opportunity to analyse patients with axSpA requiring joint replacement surgery. A detailed analysis was undertaken to determine trends in disease and baseline demographics of patients with axSpA requiring joint replacement surgery.

MATERIALS AND METHODS

Patients requiring joint replacement surgery were compared to the rest of the ASRI cohort. Baseline demographics, as detailed in Table 1, were compared between the groups. In addition, scores of disease activity and functional impairment (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], Bath Ankylosing Spondylitis Functional Index [BASFI], The Health Assessment Questionnaire [HAQ], the Ankylosing Spondylitis Quality of Life questionnaire [ASQoL], and Bath Ankylosing Spondylitis Metrology Index [BASMI]) were analysed.

Table 1: A comparison of patients with axial spondyloarthropathy requiring/not requiring joint replacement surgery, using The Ankylosing Spondylitis Registry of Ireland (ASRI) dataset.

	Joint replacement (n=33)	No joint replacement (n=827)	p value
Age (years)	55.3	45.1	**<0.01**
Disease duration (years)	31.6	18.3	**<0.01**
Delay to drug treatment (years)	6.97	7.97	0.51
HLA-B27+	94.7% (18)	71.9% (491)	**<0.01**
Males	78.8% (26)	64.7% (535)	0.76
Females	21.2% (7)	19.3% (160)	0.76
Mean Score			
BASDAI	4.91	4.06	**0.06**
BASFI	5.67	3.64	**<0.01**
HAQ	0.90	0.54	**<0.01**
ASQoL	7.42	6.67	0.45
BASMI	6.07	3.94	**<0.01**
Medication			
NSAID	51.5% (17)	47.0% (389)	0.21
Biologic therapy	72.7% (24)	57.2% (473)	0.9
DMARD	33.3% (11)	15.7% (130)	0.1

ASQoL: The Ankylosing Spondylitis Quality of Life questionnaire; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; DMARD: disease-modifying antirheumatic drugs; HAQ: Health Assessment Questionnaire; HLA-B27: human leukocyte antigen-B27; NSAID: nonsteroidal anti-inflammatory drugs.

An independent, two-tailed t-test was used to determine statistical significance between the groups. Further analysis on sex, human leukocyte antigen (HLA)-B27 status, comorbidities, and medication exposure was performed using a chi-squared test for independence. A p value of <0.05 was deemed significant.

RESULTS

In total, 33 (3.8%) of the 860 ASRI patients underwent joint replacement surgery. These patients were noted to be significantly older than the rest of the cohort (55.3 versus 45.1 years; p<0.01), with a longer disease duration (31.6 versus 18.3 years; p<0.01) and higher rates of HLA-B27 positive tests (94.7% versus 80.2%; p<0.01). No significant differences were found between the sexes (Table 1).

A number of comorbidities were analysed: patients requiring joint replacement had higher rates of all test comorbidities, with the exception of tuberculosis, chronic lung disease, and depression. No significant difference was found between medication exposure rates, although the joint replacement population did have higher rates of nonsteroidal anti-inflammatory drugs, synthetic disease-modifying antirheumatic drugs (sDMARD), and biologic therapy usage than the rest of the population; however, this did not reach significance.

These patients also achieved poorer scores for all measures of disease activity, although this only reached significance in the BASFI (5.67 versus 3.64; p<0.01), HAQ (0.9 versus 0.54; p<0.01), and the BASMI (6.07 versus 3.94; p<0.01).

CONCLUSION

Patients requiring joint replacement surgery, although few in number, represent a cohort with significantly impaired function and quality of life.

This is likely because these patients were older with more established disease. It is therefore not surprising that this cohort had higher rates of several comorbidities and significantly worse spinal mobility.

As registries continue to develop, it will be interesting to see if rates of joint replacement surgery will decline with increased use of biologic therapy at an earlier stage of disease. This will help to differentiate patients requiring joint replacement surgery caused by underlying inflammatory arthritis and osteoarthritis.

World Young Rheumatic Diseases (WORD) Day: The First International Awareness Day for Paediatric Rheumatic Diseases

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Keywords: Awareness, campaign, paediatric rheumatic diseases, World Young Rheumatic Diseases (WORD) Day.

Citation: EMJ Rheumatol. 2020;7[1]:52-54. Abstract No: AR2.

INTRODUCTION

A summary of the first international awareness day for paediatric rheumatic diseases was presented as a webcast during the EULAR E-Congress of Rheumatology on 5th June 2020. Paediatric rheumatic diseases encompass a spectrum of musculoskeletal and connective tissue conditions which affect children and young people in many ways at a crucial time in their lives. Delays to diagnosis can have a significant impact on children and young people's lives now, and in the future, and are reported around the world.[1-3] It is also known that there is a lack of awareness of paediatric rheumatic diseases amongst the general public and certain groups of healthcare professionals, including primary care physicians.[4]

METHODS

To help improve international awareness and understanding of paediatric rheumatic diseases, World yOung Rheumatic Diseases (WORD) Day[5] was established on 18th March 2019. Its aim was to raise awareness of paediatric rheumatic diseases and the importance of timely referral, early diagnosis, and access to appropriate treatment and support. A steering committee consisting of patients, parents/carers, healthcare professionals,

and researchers was established, and an external agency provided digital support. A social media campaign was launched in December 2018 to promote WORD Day, and analytics were used to measure its impact. Dissemination of WORD Day was achieved by engaging healthcare professional and patient/parent networks, as well as utilising social media to widen the reach of WORD Day.

RESULTS

Face-to-face and virtual events took place in 34 countries across six continents on or around WORD Day 2019 (Figure 1). Such events included lectures, workshops, social gatherings, sponsored activities, and media appearances. A total of 2,585 and 660 individuals followed the official Facebook and Twitter accounts, respectively, up until WORD Day. The official #WORDDay2019 hashtag was seen by 533,955 unique accounts on 18th March 2019 alone, with 3.3 million impressions.

WORD Day 2019 was the first international campaign focussed solely on children and young people with paediatric rheumatic diseases. Individuals and organisations around the world were inspired to take action, no matter how small.

Organic and funded social media content further aided the dissemination of the WORD Day message, with Facebook proving to be a popular platform to disseminate messages. Despite a wealth of different published content and authentic materials, videos proved to be the most popular with users, particularly when featuring material designed by and with children and young people. It demonstrated that despite awareness events often being resource-light, they can be implemented across a range of diverse settings.

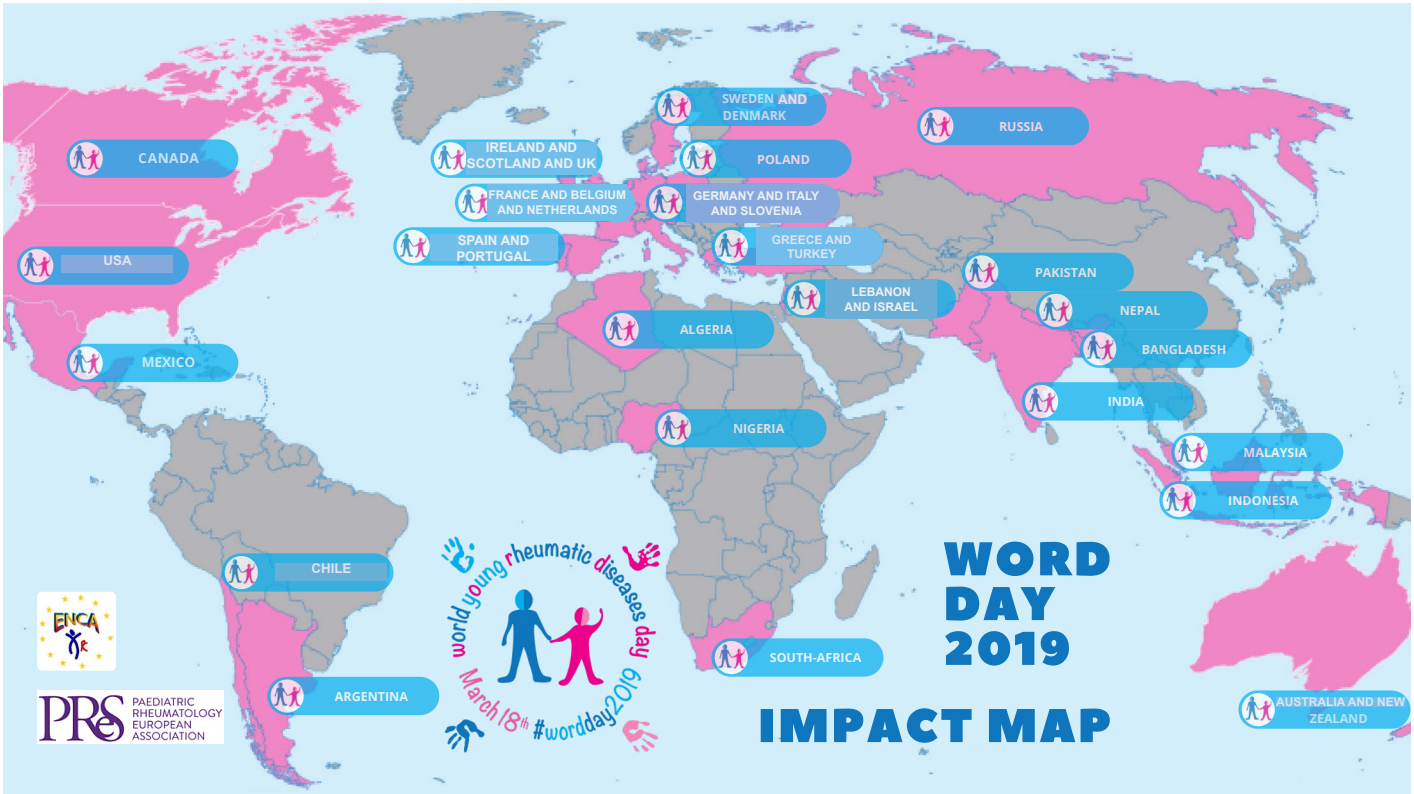

Figure 1: WORD Day 2019 map of impact.

Countries participating in the first WORD Day, March 18th 2019.
WORD: World yOung Rheumatic Diseases.

CONCLUSION

WORD Day has now become an annual global awareness event taking place on March 18th, facilitated by a growing network of patient, parent, and professional community supporters. Everyone is invited to get involved in celebrating WORD Day and raising much-needed awareness of paediatric rheumatic diseases in every corner of society.

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Predicting Rheumatoid Arthritis Using the Symptoms in Persons at Risk of Rheumatoid Arthritis (SPARRA) Questionnaire

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Keywords: At-risk, prediction, rheumatoid arthritis (RA), symptoms.

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BACKGROUND AND AIMS

Accurate prediction of rheumatoid arthritis (RA) development in persons at risk of RA can help to select individuals for early intervention trials. Currently, RA prediction mostly relies on biomarkers such as genetic factors, autoantibodies, and imaging abnormalities, with symptoms being only a minor component.[1-3] However, at-risk individuals exhibit a high prevalence of diverse, and often severe, symptoms[4,5] and information on the predictive ability of individual symptoms or symptom complexes is still largely lacking. In this prospective cohort study, the authors investigated the predictability of symptoms in persons at risk of RA, using the validated Symptoms in Persons at Risk of Rheumatoid Arthritis (SPARRA) questionnaire.

METHODS AND RESULTS

Individuals from four cohorts from the Netherlands (n=122), UK (n=77), Sweden (n=13), and Switzerland (n=20), were asked to fill out the SPARRA questionnaire, consisting of 69 questions described by van Beers-Tas MH et al.[6]

Individuals were anticitrullinated protein antibody (ACPA) and/or rheumatoid factor-positive (n=135), had relevant symptoms (arthralgia suspicious for progression to RA) with or without antibodies (n=77), or were first-degree relatives of patients with RA (n=20; excluded from primary analyses). Follow-up was ≥ 24 months. Univariable analyses preselecting possible predictors (Cox

regression; p<0.2) were followed by stepwise forward selection (p<0.1) to create a multivariable prediction model. The likelihood ratio test was used to test the added value of the SPARRA items over the clinical prediction model by van de Stadt et al.[3]

In total, 232 patients were included, 69% were female and the mean (standard deviation) age was 51 years old (13.3). Fifty-eight persons (25%) developed clinical arthritis (n=23, 26, 7, and 2, respectively, in the four groups) after a median of 7 months (interquartile range: 5.3–17.8). In total, 22 SPARRA questions were preselected and entered in the stepwise forward selection procedure. The symptoms that predicted time to development of arthritis are shown in Table 1. The symptom 'pain that moves from one side to the other' showed added value to the van de Stadt model in predicting arthritis (likelihood test, p=0.032). The area under the curve of the extended prediction model at 2 years follow-up was 0.73 versus 0.71 (area under the curve van de Stadt model without SPARRA item).

CONCLUSION

Specific symptom details such as pain moving from one side to the other or degree of joint swelling provide useful additional information to estimate a person's RA risk. The authors are currently creating a shortened version of the SPARRA questionnaire. Its systematic use in prospective at-risk cohorts will enable homogenous symptom data collection which will further improve understanding of the prevalence and predictive ability of greatly diverse symptoms in different at-risk populations.

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Table 1: Multivariable prediction model of the Symptoms in Persons at Risk of Rheumatoid Arthritis (SPARRA) questions to predict clinical arthritis.

	B	HR; (95% CI)	p-value
Does your joint pain move from joint to joint?			
Nonmoving, from arms to legs, from legs to arms (reference)	1	1	
From one side to the other	0.98	2.66; (1.47-4.84)	0.001
Over the past month how many days of the month have you had fatigue?			
0 (reference)	1	1	
1–5 days	-0.79	0.46; (0.19-1.08)	0.073
6–15 days	-0.98	0.38; (0.16-0.91)	0.029
16–30 days	-0.98	0.38; (0.19-0.80)	0.010
Over the past month how much joint swelling have you had?			
None or mild (reference)	1	1	
Moderate or severe	1.07	2.92; (1.52-5.62)	0.001

95% CI: 95% confidence interval; HR: Hazard ratio.

Are Coping Strategies, Anxiety, and Depression Associated with Daily Physical Activity in Patients With Axial Spondyloarthritis?

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Keywords: Axial spondyloarthritis (axSpA), coping, depression, physical activity.

Citation: EMJ Rheumatol. 2020;7[1]:56-58. Abstract Review No. AR4.

BACKGROUND AND AIM

Patients with axial spondyloarthritis (axSpA) who are more physically active experience less pain and better physical functioning.[1] It is also known that psychological factors such as anxiety and depression are associated with physical functioning and reduction of quality of life (QoL).[2] Furthermore, evasive coping strategies are commonly used in health-related coping.[4] However, to the best of the authors' knowledge, no data are available regarding the influence of coping strategies, anxiety, and depression on daily physical activity in axSpA. The aim of this study was to determine if coping strategies, anxiety, and depression are associated with daily physical activity in patients with axSpA.

MATERIALS AND METHODS

Consecutive outpatients from the Groningen Leeuwarden AxSpA cohort (GLAS) participated in this study. In addition to the standardised follow-up assessments, patients completed the axSpA-Short Questionnaire to Assess Health-enhancing physical activity (axSpA-SQUASH), the Coping with Rheumatic Stressors (CORS), and the Hospital Anxiety and Depression Scale (HADS). Univariate and multivariate linear regression analyses were performed to explore associations of copings strategies, anxiety, and depression, and patient- and disease-related factors with daily physical activity. Additionally, patients were stratified into three tertiles of physical activity: low, intermediate, and high. To identify group differences, the Kruskal–Wallis or chi-square test were used with post hoc testing.

RESULTS

In total 85 patients were included; 59% were male, the mean age was 49±14, the median symptom duration was 19.5 years (interquartile range (IQR): 12.0–31.0), 71% were human leukocyte antigen-B27 positive, and the mean Ankylosing Spondylitis Disease Activity Score (ASDAS) was 2.1 (standard deviation: 1.0). (Table 1). Median axSpA-SQUASH total physical activity score was 9,406.3 (IQR: 5,538.8–12,081.3). Scores of HADS-Anxiety (scale 7-28) and HADS-Depression (scale 7-28) had median scores of 5.0 (IQR: 3.0–7.0) and of 3.0 (IQR: 2.0–5.5). The most used coping strategies was comforting cognitions (for pain; range: 9–36) with a median of 25.5 (IQR: 22.0–28.0).

Univariate analysis showed that lower daily physical activity was significantly associated with female sex, higher disease activity (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]), worse physical function (Bath Ankylosing Spondylitis Functional Index [BASFI]), worse QoL (Ankylosing Spondylitis Quality of Life [ASQoL]), coping strategies such

as 'decreasing activities' and 'pacing', higher depression score (HADS), and higher perceived influence of axSpA on general well-being. In the multivariate linear regression model, the coping strategy of decreasing activities (β: -376.4; 95% confidence interval: -621.9 to -130.8; p=0.003) and BMI (β: -235.5; 95% confidence interval: -450.9 to -20.0; p=0.03) were independently associated with physical activity. The multivariate model explained 22% of variance (R^2: 0.2197; p=0.001). Additionally, patients in the highest physical activity tertile were significantly more often male, had higher working status, lower BASDAI and ASDAS, better BASFI and ASQoL, and scored lower on the coping strategy of decreasing activities.

CONCLUSIONS

In this cross-sectional study in patients with established axSpA disease, multiple patient- and disease-related factors were associated with daily physical activity. The evasive coping strategy of decreasing activities and BMI were independently associated with the level of physical activity.

Table 1: Differences between the low-, intermediate-, and high-physical activity tertiles.

		Lowest (n=27) Range: 1,030–6,075	Moderate (n=27) Range: 6,210–10,370	Highest (n=28) Range: 10,725–21,585
Age (years)		48.5±14.6	50.8±14.0	46.4±12.8
Sex (male), n (%)		14 (52.0)	15 (55.6)	21 (75.0)
Working status (working), n (%)		**9 (35.0)***	15 (55.6)	24 (86.0)
BMI (kg/m^2)		**27.9 (26.3–30.8)*†**	26.1 (23.7–30.3)	25.7 (22.7–27.8)
BASDAI (0-10)		**5.1 (3.4–6.8)*†**	3.0 (1.1–4.9)	2.2 (1.4–5.2)
ASDAS		**2.6 (1.9–3.1)*†**	1.9 (1.0–2.8)	2.1 (1.1–2.7)
CRP (mg/L)		1.8 (0.8–3.2)	2.8 (1.1–10.0)	1.2 (0.7–4.3)
BASFI (0-10)		**4.8 (2.6–7.0) *†**	2.1 (0.7–4.7)†	2.7 (1.0–4.0)
Disease influence on well-being (0-10)		**6.0 (4.0–8.0)*†**	3.0 (1.0–5.0)	3.0 (1.0–6.0)
ASQoL (0-18)		**9.3 (3.3–13.0)*†**	3.6 (0.0–8.1)	4.0 (1.0–6.9)
HADS	Anxiety (0-21)	**5.0 (4.0–10.0)*†**	4.0 (2.0–5.0)	4.0 (2.0–6.0)
	Depression (0-21)	**5.0 (3.0–9.0)*†**	2.0 (1.0–4.0)	3.0 (2.0–4.3)
CORS	Comforting cognitions	25.5 (22.8–28.0)	26.0 (21.0–28.0)	25.0 (23.0–30.0)
	Decreasing activities	**21.0 (18.0–23.3)*†**	17.0 (13.0–20.0)	16.0 (14.0–18.0)
	Diverting attention	19.0 (14.8–21.0)	19.0 (14.0–21.0)	19.0 (16.0–20.0)
	Optimism	15.0 (13.0–16.0)	15.0 (13.5–17.0)	15.5 (13.0–17.0)
	Pacing	**27.2 (23.8–30.3)***	22.0 (20.0–28.0)	22.0 (17.0–26.0)
	Creative solution seeking	21.0 (18.0–23.0)	20.0 (15.6–22.0)	19.0 (17.0–24.0)
	Accepting one's dependence	13.5 (11.8–16.0)	11.0 (8.5–14.5)	12.0 (10.0–16.0)
	Showing consideration	16.0 (15.0–18.0)	16.0 (13.0–17.0)	17.0 (14.0–18.0)

Data presented as number of patients (%), mean ± standard deviation, or median (interquartile range).

* p≤0.05 for highest group compared to lowest group.

† p≤0.05 for intermediate physical activity group compared to lowest physical activity group.

ASQoL: Ankylosing Spondylitis Quality of Life; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CORS: Coping with Rheumatic Stressors; CRP: C-reactive protein; HADS: Hospital Anxiety and Depression Scale.

These findings suggest that to improve daily physical activity in patients with axSpA, attention should be paid not only to targeting disease activity, but also to other patient- and disease-related aspects, especially coping strategies used.

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Improving Risk-Stratification of Patients with Rheumatoid Arthritis for Interstitial Lung Disease

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Keywords: Biomarker, interstitial lung disease (ILD), rheumatoid arthritis (RA).

Citation: EMJ Rheumatol. 2020;7[1]:58-60. Abstract Review No. AR5.

BACKGROUND AND AIMS

Interstitial lung disease (ILD) is a common pulmonary manifestation of rheumatoid arthritis (RA). It has emerged in recent studies as a key prognostic factor and affects rate of survival. The big challenge for rheumatologists is now the risk-stratification of patients with RA for ILD. Chest high-resolution CT (HRCT) is the gold standard for RA-ILD diagnosis, but costs and ionising radiation may limit its use in clinical practice. Thus, circulating biomarkers could aid in this risk-stratification. The authors' objective was to evaluate the merit of three circulating markers for the diagnosis and the progression of RA-ILD.

MATERIALS AND METHODS

The study included consecutive patients with RA, >18 years of age, from three tertiary rheumatology centres (Paris, France; Tokyo, Japan; and Zurich, Switzerland) over a 36-month period. All patients had at least one chest HRCT during the inclusion period. In the subset of French patients with ILD, HRCT lung images were obtained both at baseline (time of blood sample collection) and at a follow-up visit. The ILD status of patients with RA was established by chest HRCT. The chest HRCT pattern was classified as usual interstitial pneumonia (UIP) or nonspecific interstitial pneumonia (NSIP) by the local radiologist. Serum levels of lung epithelial-derived surfactant protein-D (SP-D), C-C motif chemokine ligand-18 (CCL-18), and Krebs von den Lungen-6 glycoprotein (KL-6) were measured by ELISA.

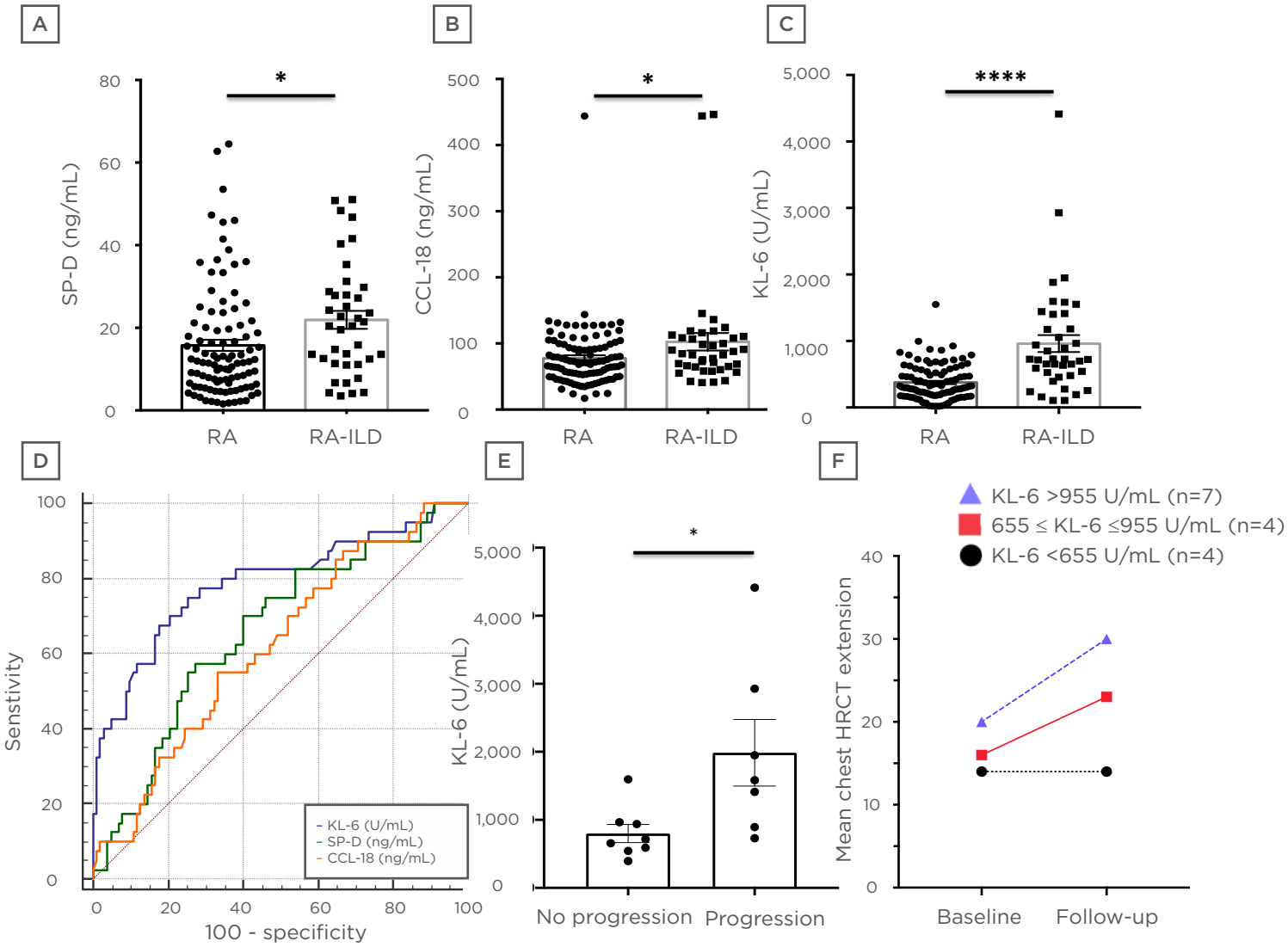

Figure 1: Concentrations of serum markers, diagnostic value, and performance of KL-6 for the progression of RA-associated ILD. **A–C)** Concentrations of SP-D (ng/mL) plus **A)** CCL-18 (ng/mL) and **B)** KL-6 (U/mL) and **C)** in patients with RA with or without associated ILD. **D)** Receiver operating characteristic curve illustrating the diagnostic value of SP-D, CCL-18, and KL-6 for diagnosis of ILD in patients with RA. **E)** Concentrations of KL-6 (U/mL) according to the progression on chest HRCT of RA-associated ILD. **F)** Degree of mean ILD progression on chest HRCT according to baseline KL-6 concentrations. The concentrations of 655 U/mL and 955 U/mL correspond to the first and second quartile of French patients with RA-ILD.

*p<0.05

**** p <0.0001 by Student's t test.

CCL-18: C-C motif chemokine ligand-18; HRCT: high-resolution CT; ILD: interstitial lung disease; KL-6: Krebs von den Lungen-6 glycoprotein; RA: rheumatoid arthritis; SP-D: lung epithelial-derived surfactant protein-D.

RESULTS

In the study, 147 patients were included (age: 66±12 years old; females: 69%; males: 31%; disease duration: 11±10 years). Amongst these patients, 40 (27%) had fibrosing ILD on HRCT, 21 had a UIP pattern, 17 HAD a NSIP pattern, and two had NSIP associated with chronic obstructive pulmonary disease.

SP-D (21.91±2.17 versus 15.76±1.34 ng/mL; p=0.017), CCL-18 (102±13 versus 78±5 ng/mL; p=0.026), and KL-6 (961±128 versus 376±26 U/mL; p<0.001) concentrations (Figure 1A-C) were significantly higher in patients with RA-ILD versus unaffected

patients with RA. KL-6 values were also higher in patients with UIP compared to the other HRCT patterns and in patients with lesion extensions >15% compared to patients with milder disease. Receiver operating characteristic curve analysis to assess the diagnostic abilities of the three markers for the diagnosis of RA-ILD showed a superiority of KL-6 (area under the curve [AUC]: 0.79; 95% confidence interval [CI]: 0.72–0.86), compared to SP-D (AUC: 0.66; 95% CI: 0.58–0.74), and CCL18 (AUC: 0.62; 95% CI: 0.53–0.70) (Figure 1D). The sensitivity of KL-6 for the diagnosis of RA-ILD was 68% with a specificity of 83%. In the French subset with longitudinal data (n=15), extension of ILD was detected in seven patients.

Baseline KL-6 serum levels were significantly increased in patients who experienced ILD progression (1,987±1,294 versus 799±375 U/mL; p=0.027) (Figure 1E). The degree of ILD progression on HRCT was also proportional to baseline KL-6 concentrations (Figure 1F).

CONCLUSION

KL-6 is relevant for the diagnosis and the prognosis of RA-ILD. It may be used as a circulating noninvasive first-line marker to stratify for indication of HRCT. Indeed, given the emerging lung issues in RA patients, this simple and highly reproducible marker, which is already available in routine care in some countries, could be a beneficial prerequisite to chest HRCT in rheumatology clinics.

2019 Update of the Joint European League Against Rheumatism (EULAR) and European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Recommendations for the Management of Lupus Nephritis

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Keywords: Lupus nephritis (LN), systemic lupus erythematosus, therapeutics.

Citation: EMJ Rheumatol. 2020;7[1]:60-61. Abstract Review No: AR6.

INTRODUCTION

A significant proportion of patients with systemic lupus erythematosus develop renal disease, which has a major impact on the course of the disease. In 2012, the European League Against Rheumatism (EULAR) and European Renal

Association–European Dialysis and Transplant Association (ERA-EDTA) developed joint recommendations for the management of lupus nephritis (LN), involving a multidisciplinary panel of physicians. Because of the emergence of new data since the original publication, the objective was to update the 2012 EULAR/ERA-EDTA recommendations for the management of LN, again with the participation of physicians from different disciplines, as well as nurses and patient representatives.

To this end, the standardised operating procedures for the publication of EULAR-endorsed treatment recommendations were followed. Expert meeting and application of Delphi-based methodology led to 15 questions for the systematic literature review, which covered essentially all aspects of LN; the systematic literature review was undertaken by three fellows.

EULAR/ERA-EDTA RECOMMENDATIONS

The main recommendations are as follows:[1] therapy in LN should aim for a complete renal response (proteinuria <0.5–0.7 g/24hours with [near-]normal glomerular filtration rate) by 12 months, although this time point can be extended in patients with significant, nephrotic-range proteinuria at baseline. Hydroxychloroquine is recommended in all patients, at a dose not exceeding 5 mg/kg/day, with regular ophthalmological monitoring. In active proliferative LN, initial treatment with mycophenolate mofetil ([MMF] 2–3 g/day, or mycophenolic acid at equivalent dose) or low-dose intravenous cyclophosphamide (500 mg x6 biweekly doses), both combined with glucocorticoids (pulses of intravenous methylprednisolone, then oral prednisone 0.3-0.5 mg/kg/day) is recommended. Alternative choices include either combination of MMF with a calcineurin inhibitor (especially tacrolimus) or high-dose cyclophosphamide, for patients with nephrotic-range proteinuria or prognostic factors for adverse long-term outcome at baseline, respectively. Subsequent, maintenance treatment with MMF or azathioprine should follow for the long-term, with glucocorticoid use minimised to the lowest possible dose (<7.5 mg/day prednisone equivalent). The choice between MMF and azathioprine will depend on the initial regimen and potential plans for pregnancy. In patients who do not respond to the recommended therapy, a switch to an alternative induction regimen or rituximab are recommended. In Class V LN, immunosuppressive therapy is indicated from the beginning in patients with nephrotic-range proteinuria or patients in whom proteinuria remains >1 g/24hours despite renin–angiotensin–aldosterone blockade; in these circumstances, MMF in combination with glucocorticoids is preferred as first choice. A repeat kidney biopsy should be considered in cases of incomplete response or nephritic flares. Belimumab may be considered as add-on treatment, in order to facilitate glucocorticoid sparing, control extra-renal lupus activity, and decrease the risk for flares. In end-stage renal disease, transplantation is the preferred kidney replacement option because of its better graft- and patient-survival rates. Relapse of LN in the transplanted kidney is rarely clinically significant.

CONCLUSION

In conclusion, the 2019 updated EULAR/ERA-EDTA recommendations serve as a guideline to inform rheumatologists, nephrologists, patient organisations, and regulators about the treatment of LN based on combined evidenced-based and expert opinion.

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Using Educational Applications to Facilitate Understanding of the Anatomy and Function of the Brain and Explore the Effects of Clinical Fatigue as from the Patient Perspective

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Keywords: Augmented reality, brain anatomy, co-design, educational application, fatigue, patient involvement.

Citation: EMJ Rheumatol. 2020;7[1]:62-63. Abstract Review No: AR7.

BACKGROUND AND AIMS

When discussing the impact of rheumatic disease states with patients living with these conditions, fatigue is often at the forefront of that discussion, as a particularly onerous symptom. In response to this, the authors sought to expand their engagement portfolio to include activities that would help the general public to better understand fatigue and the significant impact it has on those affected. To this end, the authors created an educational application utilising augmented reality and animated videos.

MATERIALS AND METHODS

The application firstly focussed on the brain, helping the user to understand that it is a highly complex organ and reinforcing that there is still much to learn, especially in its role in fatigue. The second part of the application was a short animation from the perspective of someone living with fatigue, explaining its debilitating nature and the severe impact it can have on quality of life.

To create a user-friendly and engaging application, the authors collaborated with Glasgow School of Art and University of Glasgow masters of science in medical visualisation and human anatomy students. The project proposal was also sent to the Glasgow Arthritis Involvement Network (GAIN) patient and public involvement group, who were invited to collaborate on the design and content of the application. In collaboration with GAIN, it was decided that the basic neuroanatomy of the brain would be introduced in three distinct layers (Figure 1A) and that the application would need to carefully guide users, making this complex information as accessible as possible.

The second major discussion point for the group was around the video that would describe the impact of living with fatigue from the perspective of someone who lives with it. Comments from the GAIN members that would be used to help others to understand the debilitating nature of fatigue can be seen in Figure 1B. It was decided that the video would emphasise the variability of fatigue from person to person, and that the tasks affected by fatigue are not limited to work-related activities or household chores, but also affect an individual's social life. Another important issue included in the animation was the fact that mental fatigue can be just as debilitating as physical fatigue. Finally, it was thought that the video should end by bringing attention back to how complicated fatigue is as a symptom and how this complexity is reflected in the functioning of the fatigued brain.

Some examples of the augmented reality brain aspects of the application can be seen in Figure

1C and some excerpts from the short animation can be seen in Figure 1D.

RESULTS

A pilot test was conducted at the Glasgow Science Centre with initial results showing promise in the applications' educational potential. The percentage of questions pertaining to the brain answered correctly increased from 36% before use to 60% after use of the application. Furthermore, the application also altered the user's perceptions of the impact that fatigue can have on quality of life: one of the key aims of the project. After using the application, opinions changed to reflect that fatigue can completely impair a person's quality of life, showing an increase in participants' understanding of the debilitating nature of fatigue.

CONCLUSION

This study was able to develop an educational application that has shown promise in helping to explain the complex and debilitating nature of fatigue, aiding understanding within the general population.

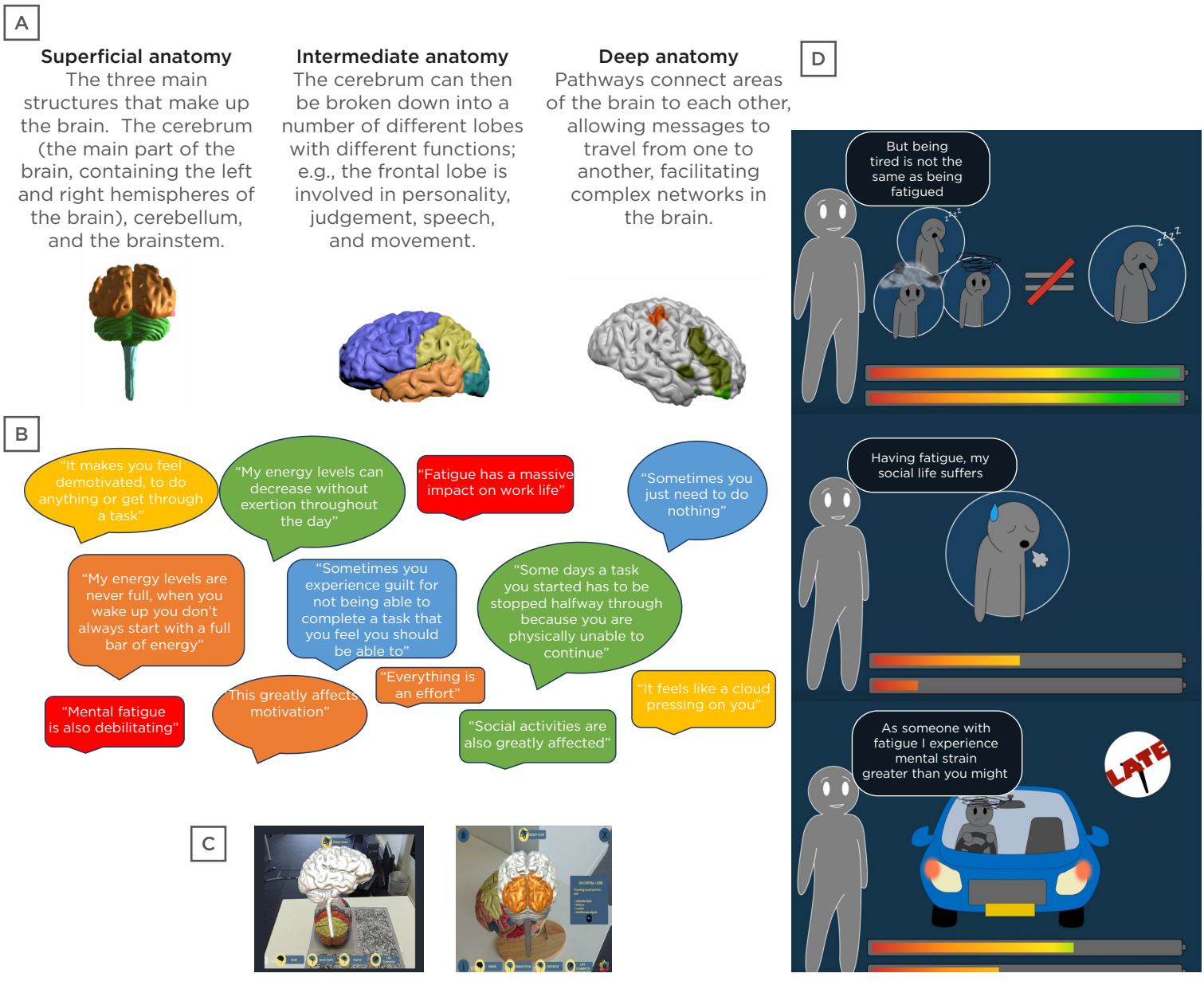

Figure 1: A) Three distinct layers of brain anatomy; **B)** Glasgow Arthritis Involvement Network (GAIN) member comments for the educational application; **C)** interface for the augmented reality brain anatomy; **D)** excerpts from the short animation surrounding fatigue.

Congress Interviews

EMJ presents interviews with the past and current Chair of the European League Against Rheumatism (EULAR) Standing Committee of Health Professionals in Rheumatology

Featuring: Dr Rikke Helena Moe and Ms Sue Oliver OBE

Dr Rikke Helene Moe

Chair of European League Against Rheumatism (EULAR) Standing Committee of Health Professionals in Rheumatology
National Advisory Unit on Rehabilitation in Rheumatology, Division of Rheumatology and Research, Diakonhjemmet Hospital, Oslo, Norway

Q1 What life decision or educational experience inspired your career choice and what do you believe are the key qualities for a successful career in rheumatology?

It was evident from the start; I knew I had to work in this field already when I was a student. The people with rheumatic diseases whom I met taught me so many things they did not know about their diseases; not just from a biomedical point of view, but about complex biopsychosocial challenges such as how best to live with their disease. Trying to help them find these answers made me aware of several unexplored areas. Rheumatology is an extremely interesting, complex, and challenging field.

For many years now I have been very fortunate to be a part of an internationally respected, multidisciplinary research group within rheumatology, and with >20 years as a physical therapist and researcher I've learnt even more about the things we do not know. Engaging with the European League Against Rheumatism (EULAR) changed my way of thinking; it gave

"Health professionals in rheumatology all over Europe have different strengths, and together we make an exceptionally skilled and strong group"

access to several networks, recommendations, educational programmes, communications, and resources that continuously opens up new possibilities of collaboration to help fill these gaps.

I believe the combination of experience, curiosity, patient partnership, engagement in national and international networks, and having a very proficient and assertive workplace are keys to a successful career in rheumatology.

Q2 What rheumatic disease do you believe merits wider attention?

In the beginning of my career, there was obviously little/no attention to the challenges of the many people with osteoarthritis. Patients kept telling us that their osteoarthritic (OA) hands were often overlooked. For the last couple of years, pharmacological and nonpharmacological treatments for osteoarthritis in general, including hand OA, have taken giant leaps forward. There is still a long way to go, but many strong research groups are focussing on taking this field further now.

Currently, it has become more and more obvious that we need more evidence on how best to treat and advise people with connective tissue diseases. Together we can help develop this field through science and education. EULAR is currently trying to facilitate initiatives and support the research groups who are currently working on this through Study Groups and Task Forces.

Q3 Your recent publication, 'Exercise and Inflammation,' discusses the possibility of exercise exerting anti-inflammatory effects. Could you please elaborate on these findings?

Historically, rest was wrongly recommended to people with rheumatic and musculoskeletal diseases (RMD), due to a fear that exercise could negatively impact disease activity. Exercise is currently one of the recommended non-pharmacological corner stones in the treatment of most rheumatic diseases. The publication referred to is a result of several collaborations within a network of clinicians and researchers who have been working to develop this field for many years. We have had an emphasis on the role of physical activity and exercise therapy in the management, prevention, and treatment of rheumatic diseases. This network has manifested as a EULAR Physical Activity and Exercise Therapy Study Group. In short, exercise is a powerful treatment for RMD.

Q4 As novel approaches to treatments emerge, the possibility of individualised medicine grows. What are your thoughts on individualising exercise therapies for the treatment of rheumatic diseases?

Everyone understands that medication must be individually tailored in order to be efficient, and the same applies to exercise. The effects of exercise for people with rheumatic diseases capture far more than general health aspects; it can help control disease and symptoms, as well as reduce the risk of comorbidity. Individually tailored exercise at the right level can improve function and physical fitness, reduce pain, depression and fatigue, help control disease and protect against comorbidity, and at the correct dosage even positively impact inflammation.

Q5 What are the main responsibilities of the EULAR Standing Committee of Health Professionals in Rheumatology (HPR), of which you are the Chair?

We are currently shaping future health care which increases the need for optimised evidence-based care, innovation, and seamless collaboration. The HPR Scientific and Educational Committees are highly motivated committees of health professionals within rheumatology (clinicians and researchers) who assist in developing, following-up on, and managing novel ideas.

Health professionals in rheumatology all over Europe have different strengths, and together we make an exceptionally skilled and strong group. We are lucky to take part in a wonderful fellowship and have colleagues to trust, cooperate with, and learn from.

Future HPR research projects are mainly aimed at: maintaining and improving individuals everyday life and participation in functional activities and society; enhancing individuals' ability to self-manage rheumatic musculoskeletal diseases; supporting individuals to stay in or return to work and education; and reducing inequality and inequity in healthcare for people with RMD.

"Engaging with the European League Against Rheumatism (EULAR) changed my way of thinking; it gave access to several networks, recommendations, educational programmes, communications, and resources"

Educational HPR projects primarily focus on: identification of HPR educational needs; a comprehensive and evidence-based core curriculum which articulates with the wider EULAR strategy and maps on to the varying needs of HPR in EULAR; a tiered competency framework to allow assessment and, as appropriate, certification against agreed standards; a creative plan for maximising access to and uptake of the resources provided by EULAR; a formal implementation plan for the strategy and associated materials; and an evaluation of the uptake and impact of the strategy.

Q6 During your term as Chair, what are the biggest accomplishments you wish to achieve, and how do you plan to contribute to the committee's goal of building an international network of excellence?

EULAR HPR conducts research that substantially impacts and significantly contributes to the knowledge and evidence base of the quality of life for people with rheumatic musculoskeletal diseases. Accessibility, equality, organisation of health care services, outcomes, and policy improvements relevant to people with rheumatic and musculoskeletal diseases, represent important areas of research.

We have developed our EULAR HPR research strategy 2018–23, with actions towards improving and sustaining quality of life for people with rheumatic musculoskeletal diseases. The current macroeconomic and geostatic mega trends point towards a shift in demography and a rise in technology that will be shaping the health care system of the future. This increases patient needs and underlines the importance of optimised evidence based care, innovation, and seamless collaboration between the health care system and other stakeholders, which has become highly visible with the current pandemic.

We in the HPR leadership, together with the committees, are trying to facilitate collaboration, networking, research, educational activities, an excellent EULAR Congress programme, Study Group activities, communication, and implementation, and to expand our project portfolio and recommendations in line with our strategy.

Q7 How did EULAR's decision to opt for a virtual congress this year impact your committee?

We were prepared for the possibility of a smaller e-congress a couple of months ahead, and appreciate taking part in this challenge. We made our priorities and contributed to a selected EULAR programme for the e-congress menu in a short amount of time, well aware that this will impact on the way we think about our congresses and sustainability in the future. I am sorry that we will not be able to physically meet at the congress in Frankfurt, but we are excited about testing this new format.

Q8 A recent publication of yours, 'Clinical Aspects of Hand Osteoarthritis,' highlights that osteoarthritis is predicted to become one of the leading causes of disability. Could you provide key takeaway messages from this book and any advice you might have for our readers?

The key messages are that it is important that people with hand osteoarthritis are offered education about their disease and how to self-manage, and that exercise and orthoses can help improve symptoms and function.

Ms Sue Oliver OBE

Past Chair of European League Against Rheumatism (EULAR) Health Professionals in Rheumatology Standing Committee

Q1 After your master's in science, healthcare, and professional issues, what sparked your interest in Chairing the Royal College of Nursing (RCN) Rheumatology Forum?

When I started my masters, I think that I was always keen to have a role where I could make a bit of a difference and so finding a way to do that felt right for me. In 2002 and 2004 before I was Chair, I was a co-opted member of the Rheumatology Forum. The forum is for nurses who are interested and want to get actively involved; there was so much going on within the field of rheumatology and it was very exciting at the time. So, there were many reasons why I wanted to be more actively involved in the Rheumatology Forum; I felt specialist nurses needed to have more power, to be recognised more within the field, but also that we needed to step up and be more actively engaged in supporting patients through many aspects of care. I learned a lot about the Forum and the RCN and how professional aspects could be developed within the RCN, before being co-opted. I really love rheumatology and I found a place that fitted well for me. I went to the 1999 American College of Rheumatology (ACR) conference, but I also went to the pre-scientific meeting which is where all the breaking news was presented. I was very lucky that I went in the year that they were introducing biologics for the first time; sitting there and listening, I thought this was a huge revolution. There was a lot of interest in biologics in the UK but also many challenges to the nurse specialist because it was a new field and we were going to be managing these patients. Lots of nurses didn't know about how to screen and assess these patients It was key to me that we had offered resources and support to nurses within the field of rheumatology.

Q2 What were the most important learnings from your clinical roles with the National Health Service (NHS) that led you to be a successful consultant for various organisations such as the Department of Health, Kings Fund, National Audit Office, and the National Institute for Health and Care Excellence (NICE)?

I left the NHS and my clinical nurse specialist role after doing quite a lot of reading about the future and how nurses could develop, guiding my decision to set up my own clinic doing consultancy work. I had quite a lot of experience because I'd already served as the Chair of the Rheumatology Forum and started representing nurses in the Department of Health and the British Society for Rheumatology (BSR), as well as being Chief Nurse Advisor for the National Rheumatoid Arthritis Society and working on guidelines for NICE. I then set up my own consultancy after conducting a nurse prescribing course and running advanced nurse-led clinics. I really wanted to expand the role of the nurse, but also be a strong role model and really test some of the new ways of going forward. When you're in a clinic you're booked for 6 weeks in advance, but because I was independent, I was flexible and able to go to meetings. I gave my time freely and was lucky because my husband was very supportive. I gave a lot of my time and energy freely because I really felt there was a vision and a need that I really wanted to build on. At the core of me is an NHS nurse, and the more I've travelled around the world the more I think the NHS is the most fabulous healthcare system.

All of these were the reasons I got involved, with the overall aim of improving care for patients. I was representing patients by working with a patient organisation and they were saying "we don't see the doctors as often as it says in the guidelines" and "we don't get access to this/that." I spoke to the chief executive of the patient organisation and said we need to do something together; we need to try and understand what's happening in our services. We got a meeting together

"I gave a lot of my time and energy freely because I really felt there was a vision and a need that I really wanted to build on"

with rheumatologists at the BSR, the patient organisations, and also the pharmaceutical industry, because they're actually very well-informed, very able, and very interested in the services. So, we managed something that I didn't think could be achieved which is to get them all sitting around a table together and agreeing to work collaboratively. This was called the Futures Forum and as a result we managed to commission a piece of research that was undertaken by the Kings Fund. So to answer your question more clearly, each of these different pieces of work gave me a greater insight into how to get all parties to work together to try and identify barriers and identify ways to improve the patients' journey through healthcare. My real key learning was to focus on the patients' journey and how to optimise that journey in the most evidence based, cost effective way.

Q3 You have been especially committed to raising awareness of chronic conditions such as rheumatoid and osteoarthritis; what are the most common patient outcomes for these diseases and how can they be improved?

When people are diagnosed with a chronic condition the diagnosis has an effect on the patient's self-esteem and it can present a challenge. It's an unspoken agenda that often society sees people with chronic conditions as different, and some patients feel that they have failed in some way. It's a challenge they have to face, so I care very much about how the diagnosis is delivered and how health professionals help those patients come to terms with their condition. The manner in which you start the journey with a new patient is vital to how they will see themselves and go forward with their disease in the future. I think that it's not only an important investment in time but also for future well-being of the individual. I've been committed to chronic disease issues because as a healthcare professional we have historically been too paternalistic and fostered reliance on healthcare rather than independence. There are many ways to encourage independence, but we need to build them into what we will deliver throughout the individual's healthcare journey. If we do that then the patient outcomes, I believe, should encompass aspects that demonstrate how empowered the individual feels, their understanding of healthcare resources and how to access them, and better knowledge of treatments. Why should I expect the patient to just take something like methotrexate because I say it's beneficial? We have to take them gently on that journey, and the skill of the health professional is in understanding our patients by getting some sense of their anxieties and learning needs as quickly as possible, as well as working with them to achieve the best outcomes for them.

Q4 Could you tell us about the rheumatology nursing educational developments that you have been supporting in Asia?

I love the Asia–Pacific region, and 18 years ago I was approached by Professor Gavin Lee who was the president of the Rheumatology Society in Hong Kong. He invited me to visit and deliver lectures and speak to some senior rheumatologists about why they should consider developing rheumatology nursing. I was so impressed with them, but also aware of the challenges when I visited a hospital in Hong Kong. I was shocked at how difficult it was for them; the clinics were huge, and patients had so little time with the doctor. It was an impossible situation to continue operating that way forever and it was going to have to change. I was keen to help and keep in touch regarding their progress, so I offered general support in little ways such as mentoring and sending information, as a result of which I was invited back several times. We were trying to develop rheumatology nursing in Hong Kong so that it would be recognised as a specialty within the nursing authorities. Our first challenge was working within the framework that would work best for Hong Kong; you have to look at the organisation and professional challenges and work with their stipulations. The rheumatology services in Hong Kong have done a great job and rheumatology nursing has now been recognised as a nursing speciality; it is really well-defined and working smoothly. I am still in regular communication and actively enjoy supporting their development as and when need.

Q5 What impact do you hope your online resources for both healthcare professionals and patients to have?

It's been a good place for Asia–Pacific healthcare professionals to get some resources. For instance, there is the Royal College of Nursing disease activity score (DAS) video which has been translated into different languages such as Chinese etc. Chiefly, I want to sign post those interested to the latest evidence-based guidelines and to organisations that offer valuable resources, providing the most up-to-date work. For example, signposting to work posted on the Asia–Pacific League Against Rheumatology (APLAR) website, which offer resources for nurses across Asia–Pacific to download. There are teach-the-teacher style programmes to support them initially, before they may move onto undertake something like the European League Against Rheumatism (EULAR) course. What I'm trying to do is encourage them in every way possible, and these are exciting projects to be part of. Supporting and offering resources to new rheumatology nurses is key to the future of the specialism. I've also just published a second edition of the Oxford University Press Musculoskeletal Handbook. I worked with some excellent contributors to get it out there and I think it is a really good resource.

Q6 Could you tell us what your role entailed whilst you served 4 years as Chair of the EULAR Healthcare Professionals Standing Committee?

It's a big organisation and you're working with many different countries. The role was really about being part of the executive team helping to form the way forward for EULAR and to provide a sense of the type of work carried out and issues facing all healthcare professionals such as nurses, physiotherapists, psychologists, occupational therapists, podiatrists, and doctors. As Chair I was representing the healthcare professionals' experiences, knowledge, and developmental needs with the context of the committee's remit. Members of the Executive Committee identify key issues that are relevant to improving patient care and help healthcare professionals in all areas to deliver evidence-based practice. The Health Professionals Standing Committee also help to form the scientific programme for EULAR each year. As chair I also focussed on encouraging more countries to join EULAR as country members in the Health Professionals category, a key issue allowing greater representation at the EULAR congress.

Q7 Were there any projects you led whilst serving as Chair that you are particularly proud of?

When you're Chair, you pick up work from the previous Chair and build on what they have done. Equally, when you walk away, it's a very humbling thing because it's as though you were never there, as the work carries on. I'm particularly proud of the fact that previously we had 10 or 12 healthcare professional organisations on the EULAR group as country members, and that's now 25. I spent a lot of time visiting other countries in Europe who wanted to join and mentored them along the route to submitting to the Executive Committee for EULAR membership.

Q8 In 2014 you were recognised in the Queen's birthday honours list and awarded an Order of the British Empire (OBE); do you think this will have raised the profile of rheumatology as a speciality?

For me it was a big surprise and I was incredibly proud. Apparently, to be able to be considered for submission you require significant support from a range of organisations before you can be considered. So, it was a very humbling experience for me because I worked in an unusual way in that I was an independent nurse consultant, working with the NHS, but also undertaking different pieces of work with different organisations. It was an unusual model compared to most other nurses. So, for me, that was a very strong endorsement of what I was doing. I hope, in some small way, it has raised the profile for rheumatology nursing, and for patients.

"I'm particularly proud of the fact that previously we had 10 or 12 healthcare professional organisations on the EULAR group as country members, and that's now 25"

Interview

Clinical Prof Daniel Wallace

Rheumatologist, Cedars-Sinai Medical Center and Ronald Reagan UCLA Medical Center, Los Angeles, California, USA

Q1 You undertook both your residency and rheumatology training at Cedars-Sinai Hospital in California, USA, and continue to work there more than 40 years later. What is it about Cedars-Sinai's healthcare community and training that has kept you there?

My father joined the staff of the old Cedars of Lebanon in Hollywood in 1947 as a cardiologist and practiced there for 60 years. He worked with Swan, Ganz, Prinzmetal and Corday (developer of the Holter monitor). The old hospital is now the world headquarters of the Church of Scientology. I was a Cedars summer intern in college and established lots of lasting friendships and relationships. After doing an internship at Brown University, it was natural to return home.

Q2 Why rheumatology? What about the specialty drew your interest, and has kept your interest throughout your clinical practice?

When I was a medical student at the University of Southern California (USC), I was inspired by Ed Dubois MD, who had the largest lupus practice in the USA and ran their lupus clinic. I became friendly with him and eventually took over his practice when he became ill. The patients were fascinating. Ed had clinic hours at 9:00 am, 10:30 am, 1:00 pm, and 2:30 pm, where he scheduled six patients for each slot. The patients bonded with each other, and fought to have a specific slot so they could go to lunch together. This eventually led to the formation of The American Lupus Society, which later merged with the Lupus Foundation of America.

Q3 You have been practising rheumatology for more than 40 years; how has practice changed in that time, and what do you think has been the greatest development in care in rheumatology?

When I was a fellow in the late 1970s, we were already using methotrexate, cyclophosphamide, azathioprine, and prednisone. Dr George Friou, who was the first to introduce anti-dsDNA and ANA to the clinic, was one my professors at USC. The lupus anticoagulant was discovered by Sam Rappaport, who was my father's medical school classmate and one of my mentors. What's new are updated serologies, biologics, more bureaucracy, less emphasis on the physical examination, and electronic medical records.

Q4 Your practice currently cares for over 1,500 patients with lupus – the largest patient cohort with lupus in the USA. How does

"In my experience and those of my colleagues, there may be less COVID-19 among our rheumatic disease patients, and their cases may be milder"

your practice best utilise this cohort for research and clinical insight?

Until about 2000, most lupus research was single-centre oriented. We have been able to leverage our cohort as part of the Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) and the Lupus Clinical Investigators Network (LuCIN: a 57-centre network in the USA and Canada), and have multiple other collaborations. Cedars-Sinai has some brilliant immunologists who we regularly work with.

Q5

You set up the Wallace Rheumatic Diseases Foundation to support research and access to clinical care for patients with rheumatological diseases. What prompted you to set up your own foundation?

Unfortunately, the US does not have universal access to health care. Our Foundation provides free rheumatologic outpatient care to uninsured and underinsured patients. Grateful patients asked for the opportunity to give back in a meaningful way. We also support research at Cedars-Sinai and summer fellowships.

Q6

On top of more than 400 publications in rheumatological research, you have written more than 30 book chapters and published eight of your own textbooks. How do you see more traditional formats like academic textbooks fitting into medical training and continuing medical education going forward, in the age of digital or online formats?

There are fewer major medical book publishers and the number of new titles being published is down by 80%. Medical journals are now owned by a handful of large conglomerates. However, this consolidation is allowing textbooks to be updated more quickly and printed a la carte, or per order rather than waiting for a new edition to come out. The new system allows for ebooks, and greater availability of specific chapters and PowerPoint slides.

Q7

You were recently in the news, discussing low rates of COVID-19 in your patients with lupus. What has been your experience of COVID-19 in this population, and what patterns have you spotted that may help inform prevention or care?

In my experience and those of my colleagues, there may be less COVID-19 among our rheumatic disease patients, and their cases may be milder. I am part of a LuCIN initiative that is currently looking into this. It may have something to do with higher levels of interferon-α among some of the patients that protects them from certain viruses, but we really don't know.

Q8

You were named one of America's Top Doctors by Castle Connolly 11 years running; 2004–2014, as well as several times since then. What about your clinical care led to this distinction in your opinion?

It's probably a measure of respect from my colleagues who do the voting. I like to think that our staff gives time and attention to more than what is covered in an office visit. We try to assist with their social needs and coping mechanisms.

Q10

Based on your experiences, what advice do you have for rheumatologists in the early days of their careers?

Decide where you want to live, and you can be successful there. If one is fulfilled and happy, then decide what your best skills are and excel in them. Never worry about anybody getting another opinion and be open minded.

Early Recognition and Treatment of Spondyloarthritis: A Timeless Challenge

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INTRODUCTION

Spondyloarthritis (SpA) is a chronic systemic rheumatic disease, the hallmark manifestation of which is inflammatory back pain, and may also involve peripheral joints. There have been important developments in SpA, from its classification to the available imaging modalities, treatment options, and outcome measures. There has been a shift in the treatment paradigm to a more treat-to-target approach, where a level of a relevant outcome of the disease (e.g., disease activity) is defined as a goal to prevent consequent disability.[1] The past typical example of a patient with SpA was a young person with irreversible deformation and functional disability that occurred over several years. Nowadays, the typical example of a patient with SpA is someone with a chronic but manageable disease who can remain active and participative. The reality is less ideal, since mandatory steps for a successful management (early recognition, referral, and treatment) are still undervalued. This review approaches the major 'checkpoints' that enable prompt and correct diagnosis and management of SpA.

HISTORICAL PERSPECTIVE AND CLASSIFICATION OF SPONDYLOARTHRITIS

For decades, SpA was a 'neglected' disease, with only some isolated case reports of patients in advanced stages of the disease. Since the 1890s, efforts were made by Bechterew, Strumpell, and Pierre Marie to define ankylosing spondylitis (AS),[2] a form of SpA characterised by radiographic sacroiliitis. Many societies attempted to develop classification criteria, drawing in new evidence from genetics, imaging, and extra-articular manifestations. Wright and Moll[3] defined seronegative spondyloarthritis (seronegative referring to the lack of rheumatoid factor) as a set of different and independent diseases with common characteristics, namely: AS, reactive arthritis, psoriatic arthritis, arthritis associated with inflammatory bowel disease (IBD), and a juvenile form of SpA. Many patients with inflammatory back pain without the typical imaging features were classified as 'undifferentiated' spondyloarthropathy in the late 1980s. However, in the early 1990s relevant

classification criteria appeared: from the modified New York (mNY) criteria for AS,[4] to the Amor et al.[5] criteria and the European Spondyloarthropathy Study Group (ESSG)[6] classification, the latter two of which addressed the whole spectrum of SpA including axial and peripheral manifestations. It was not until the 21st century that the Assessment of Spondylo Arthritis international Society (ASAS) group developed the ASAS classification criteria, which acknowledges SpA as a heterogeneous family that includes two distinct phenotypes: a predominant axial and a predominant peripheral form.

Table 1: Comparing classification diagnosis criteria for spondyloarthritis.

	mNY	Amor et al.[5]	ESSG	ASAS	
				Axial	Peripheral
Date initiated	1984	1990	1991	2009	2011
Entry criteria	Not required	Not required	Synovitis or IBP	≥3 months back pain and age at onset ≤45 years	Cannot meet ASAS axSpA criteria nor have current IBP + Arthritis, enthesitis, or dactylitis
Imaging	Radiography (mandatory)	Radiography (included but not mandatory)	Radiography (included but not mandatory)	Radiography and MRI are part of the criteria*	
Inflammatory markers (CRP)	Not assessed	Not assessed	Not assessed	Part of the criteria*	
HLA-B27	Not assessed	Part of the criteria*	Not assessed	Part of the criteria*	
Score composition	3 clinical criteria plus 1 imaging criteria AS if: Radiological criteria + ≥1 (out of 3) clinical criteria	Group into clinical, radiological, genetic and response criteria Different weights but no mandatory criteria or hierarchy SpA if: Sum ≥6 present Sum ≥5 probable (0–20)	2 mandatory variables (at least 1) + Set of 7 accessory variables SpA if: One of the two entry criteria + ≥1 (out of 7) accessory variables	Imaging arm: sacroiliitis on imaging + ≥1 SpA feature (out of 11) ≥2 SpA feature (out of 11)	≥1 SpA feature** (uveitis, psoriasis, IBD, previous infection, HLA-B27, or sacroiliitis on imaging) dactylitis, IBP ever, family history for SpA)

Table 1 continued.

	mNY	Amor et al.[5]	ESSG	ASAS	
				Axial	Peripheral
Specific features	Only applies to r-axSpA/AS (no peripheral involvement assessed)	Originally classifies patients as having SpA, regardless of axial or peripheral involvement, or presence of imaging/ radiographic features		Allows classification as pSpA or axSpA axSpA classified into imaging or clinical arm axSpA imaging arm can be further classified as r-axSpA versus nr-axSpA	

AS: Ankylosing spondylitis; ASAS: The Assessment of SpondyloArthritis international Society criteria; axSpA: axial spondyloarthritis; CRP: C-reactive protein; ESSG: European Spondylarthropathy Study Group criteria; HLA-B27: Human leukocyte antigen-B27; mNY: modified New York criteria; nr-axSpA: nonradiographic axial spondyloarthritis; pSpA: peripheral spondyloarthritis; r-axSpA: radiographic axial spondyloarthritis; SpA: spondyloarthritis; IBP: Inflammatory back pain.

*Even though it is possible to classify patients without these, many patients may be left unclassified in many situations if imaging and/or HLA-B27 status is lacking. Therefore, these are strongly recommended.

**SpA features (for axSpA): inflammatory back pain, arthritis, heel enthesitis, uveitis, dactylitis, psoriasis, inflammatory bowel disease, good response to NSAID, family history of spondyloarthritis, HLA-B27, and elevated C-reactive protein.

These criteria mainstreamed the concept of nonradiographic axial SpA (nr-axSpA) to define patients with axSpA without substantial radiographic sacroiliitis (as in classical AS) and also allowed the classification of a patient by imaging features or by clinical features only (Human leukocyte antigen [HLA]-B27] positive with two more features, regardless of imaging). nr-axSpA patients meet the ASAS criteria for axSpA but do not have radiographic sacroiliitis. Besides the classical radiographic findings used in the pre-existing mNY criteria, it also integrated MRI. MRI gives the possibility of identifying earlier stages of the disease (inflammation), other than the classical radiographic findings, reducing diagnostic delay. Table 1 shows the main features and differences of the main classification criteria for SpA.

ASAS criteria moved from the concept of independent but related clinical entities (as in the Wright and Moll[3] categories) into a concept of inter-related clinical manifestations. Classification criteria are not diagnostic criteria, although very often incorrectly used for diagnosis. Interestingly, there is no difference in the prevalence of axSpA between the sexes, although studies have identified male sex as a risk factor for radiographic progression, as well as HLA-B27, smoking, and mechanical stress. Evidence suggests that only some patients with nr-axSpA, especially if male, will evolve to AS.

DISEASE DIMENSIONS AND KEY MEASURES

In order to treat-to-target it is essential to have an objective target. In the 1990s, the first disease-specific validated, compound patient-reported outcome for disease activity to become available was the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),[7] composed of six questions assessing fatigue, axial and peripheral pain/tenderness, and stiffness in a numeric scale.

Table 2: Spondyloarthritis dimensions and respective outcome measures.

Assessed dimension	Score	Relevant information
Disease activity	BASDAI (0–10) ASDAS	6 patient reported item 4 patient reported items, systemic inflammation marker
Disease specific functioning	BASFI (0–10)	10 item patient reported questionnaire
Disease specific structural impact	BASMI (0–10)	Scored by the clinician during physical examination
Disease specific QoL	ASQoL (0–18)	18 item patient reported questionnaire
General QoL	SF 36 – PCS (0–100) SF 36 – MCS (0–100)	Set of multidimensional patient-reported questionnaires
Fatigue (nonspecific)	FACIT-F (0–52)	13 item patient-reported questionnaire
Anxiety and depression (nonspecific)	HADS-D (0–21) HADS-A (0–21)	14 item patient-reported questionnaire (common questionnaire divided during scoring by anxiety and depression dimensions)
Joints count	SJC 0/44 (0–44) TJC 0/44 (0–44)	Scored by the clinician during physical examination
Enthesis	SPARCC enthesitis index (0–16) MASES (0–13)	Scored by the clinician during physical examination
Structural damage	mNY score (0–8; or binary)	Images scored by a trained reader
Radiographic progression spine	mSASSS (0–72) CTSS (0–552)	Images scored by a trained reader
Acute local inflammation (MRI)	SPARCCC (0–72) for SIJ SPARCCC (0–108) for spine	Images scored by a trained reader
Structural damage (MRI)	SPARCCC-SSS (0–40 or 0–20 according to the assessed lesion)	Images scored by a trained reader
Systemic inflammation (nonspecific)	ESR (mm/h) CPR (mg/L or mg/dL)	Objective biochemical marker
Health status (specific)	ASAS-HI (0–17)	17 questions patient-reported
Health status (nonspecific)	Eq5D (utility scale: -1 to +1) EQ-VAS (0-100)	Patient-reported (different versions available)
Patient global assessment	PGA (0–10)	1 patient reported item
Physician global assessment	PhGA (0–10)	1 physician reported item
Response criteria	ASAS 20 improvement criteria ASAS 40 improvement criteria ASAS 5/6 improvement criteria ASAS partial remission BASDAI 50	Binary compound indexes Multidimensional scores that blend patient reported, physician reported, and/or inflammatory markers

ASAS-HI: Assessment of SpondyloArthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Function Index; BASMI: Bath Ankylosing Metrology Index; CRP: C-reactive protein; CTSS: CT Syndesmophyte Score; ESR: Erythrocyte Sedimentation Rate; Eq5D: Euroqol 5 dimensions; EQ-VAS: Euroqol visual analogue scale; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HADS-A: Hospital Anxiety and Depression Scale anxiety; HADS-D: Hospital Anxiety and Depression Scale depression; MASES: Maastricht Ankylosing Spondylitis Enthesitis Index; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; SF36-MCS: Short Form Survey 36 items mental component score; SF36-PCS: Short Form Survey 36 items physical component score; SPARCC: Spondyloarthritis Research Consortium of Canada; SPARCC-SSS: Spondyloarthritis Research Consortium Of Canada MRI Sacroiliac Joint Structural; SJC: swollen joint count; TJC: tender joint count.

Decades later, a more sensitive disease activity measure appeared: the Ankylosing Spondylitis Disease Activity Score (ASDAS), based on three questions from the BASDAI, with patient global assessment and systemic inflammatory markers. Functioning is another central dimension in SpA. It is not infrequent that a patient with long-standing symptoms and structural damage may still have impaired functioning (measured by the Bath Ankylosing Spondylitis Function Index [BASFI]), regardless of acute inflammation caused by structural damage. Structural impact over the sacroiliac joints as well as over the spine is a central feature in SpA. Besides the classical scores for radiographic structural progression, such as the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), new validated inflammation/damage scores using MRI (e.g., the Spondyloarthritis Research Consortium of Canada [SPARCC] scoring system) and CT (e.g., CT Syndesmophyte Score [CTSS]) have been validated and implemented in randomised control trials. However, MRI does have its disadvantages. It is an expensive technique, not universally available, many patients have contraindications, and some patients are not suitable for scanning because of claustrophobia or discomfort after a long time in the decubitus position.

Disease impact is not just limited to physical dimensions as the impact on overall health status is also crucial, leading to the development of the ASAS Health Index (ASAS-HI). The ASAS-HI is a 17 question-based compound patient-reported outcome that assesses the impact of SpA in different health dimensions, such as daily activities, fatigue, and interpersonal interactions.[8] The main outcomes for the different dimensions are summarised in Table 2. The ASAS group developed a set of disease-specific quality standards to help improve the quality of healthcare provided to patients.[9]

Considering the societal impact of SpA, studies such as the ASAS-Comorbidities in SpondyloArthritis (ASAS-COMOSpA) initiative demonstrated that disease activity is associated with poorer work participation (absenteeism and presenteeism), regardless of the clinical phenotype (radiographic or nonradiographic).[10] This suggests that the better the disease activity control, the better the work participation.

TREATMENT RECOMMENDATIONS AND TREAT-TO-TARGET

For patients with active axial manifestation, current guidelines recommend nonsteroidal anti-inflammatory drugs (NSAID) at maximum tolerated dosage as first-line treatment. If there is a failure of response to two different NSAID after 4 weeks (in total), then a biologic disease-modifying anti-rheumatic drug (bDMARD) must be considered.[11] The bDMARD may be a TNF inhibitor or an IL17 inhibitor. There is some evidence on the inhibition of radiographic progression by TNF.[12] JAK inhibitors are a possible option, remaining controversial because of limited evidence.[13] Treatment tapering remains another controversial issue because of conflicting and limited evidence.[11-13]

There is no satisfactory evidence in favour of oral steroids or conventional synthetic DMARD (csDMARD) in axial disease. Patients with r-axSpA or nr-axSpA must be treated as soon as possible to improve disease activity levels and function.[14] Physical activity and physical therapy should be considered on a case-by-case basis.[11-13]

For peripheral manifestations, a csDMARD can be useful (e.g., sulfasalazine). Patients with active IBD, uveitis, or psoriasis should be referred to the respective specialty department. Figure 1 shows extracts from the latest treatment recommendations of the European League Against Rheumatism (EULAR). Current treat-to-target recommendations state: "The goals of treating the patient with SpA or psoriatic arthritis are to optimise long-term health-related quality of life and social participation through control of signs and symptoms, prevention of structural damage, normalisation or preservation of function, avoidance of toxicities, and minimisation of comorbidities."[1]

The ideal goal should be sustained inactive disease/remission (ASDAS: <1.3 for axial manifestations), or at least low disease activity (ASDAS: <2.1). Although the ASAS improvement and partial remission criteria are widely used in randomised control trials, these are less discriminative than the respective ASDAS categories. Ideally, the target should include composite measures of disease that include clinical features, objective measures of inflammation, function, quality of life, and radiographic progression.

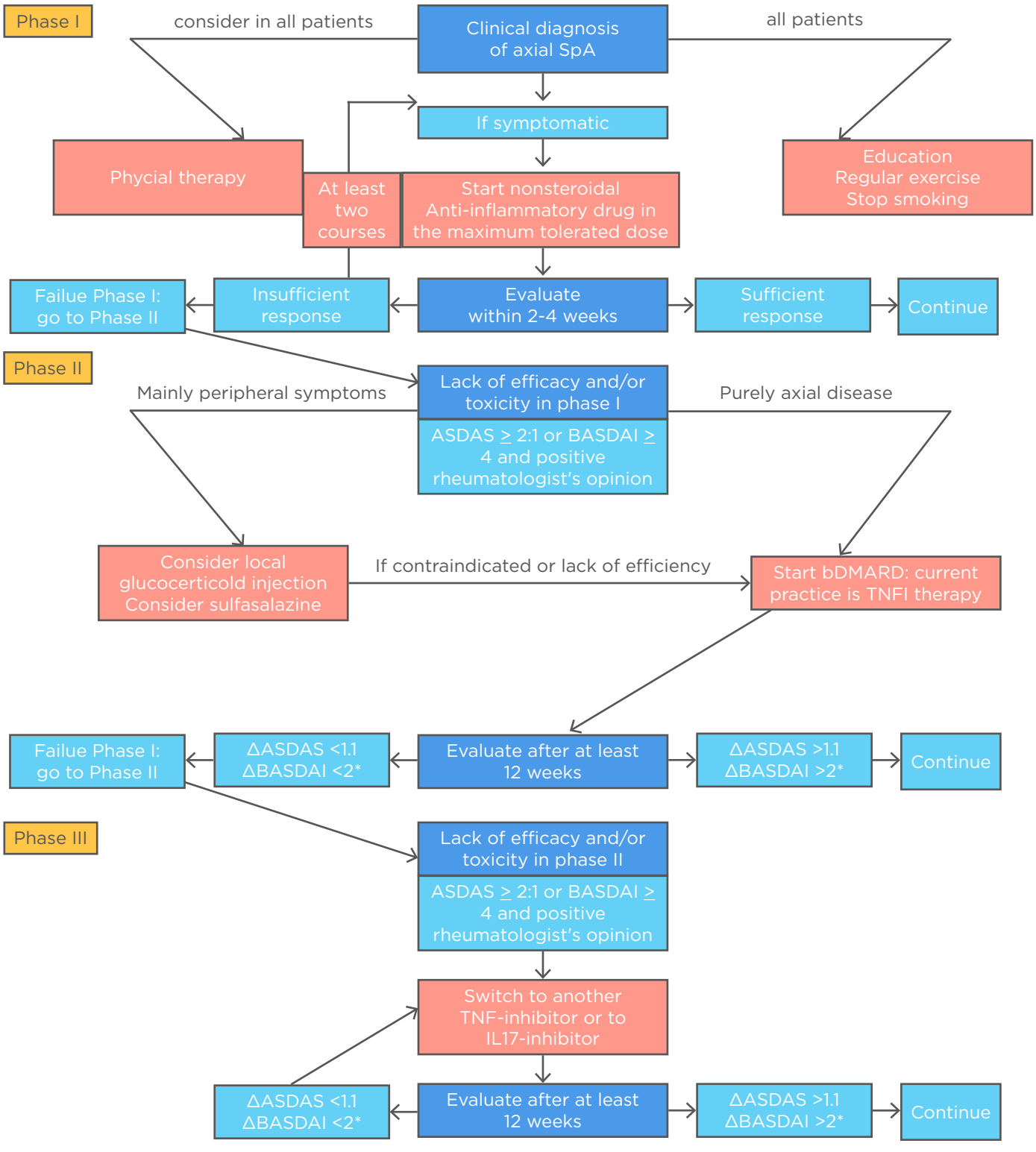

Figure 1: Algorithm based on the ASAS-EULAR recommendations for the management of axial spondyloarthritis.

ASAS: Assessment of SpondyloArthritis international Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; bDMARD: biological disease-modifying antirheumatic drug; EULAR: the European League Against Rheumatism; IL17-inhibitor, interleukin-17 inhibitor; TNFi: tumour necrosis factor inhibitor.

*Either BASDAI or ASDAS, but the same outcome per patient.

Reproduced from *van der Heijde D et al.*[11]

However, disease activity measures such as BASDAI and ASDAS do not consider all domains, especially extra-articular manifestations.[14] Treat-to-target is based on the idea that the sooner the treatment is implemented, the lesser the disease progression and impairment; it was created by evidence extrapolated from psoriatic arthritis.[1]

OBSTACLES TO EARLY REFERRAL AND ADEQUATE TREATMENT

Since back pain is a very common symptom and SpA is a relatively rare disease, many patients overlook their symptoms and report them late. Many general practitioners may be unaware of the inflammatory characteristics of back pain as well as the extra-articular manifestations of axSpA. Even in developed countries such as Germany or the UK there is a median delay from symptom onset to clinical diagnosis of 2–5 years, which does not appear to have reduced over the last few years.[15,16] Important clinical factors behind this delay included female sex, negative HLA-B27 status, presence of psoriasis or uveitis, and younger age at symptom onset. However, the presence of arthritis was associated with an earlier diagnosis.

Even after a correct diagnosis and referral, access to treatment is also a major issue in developing countries. The ASAS-COMOSpA initiative reported an unequal selection of treatment for SpA across different countries, regardless of clinical indication. In some countries, patients may be on ineffective csDMARD as an alternative to bDMARD, which has proven evidence, because of lack of access.[17]

CLINICAL CASE OF A HISTORICAL EXAMPLE

Herein the authors present the case of a 30-year-old female who visited her physician in the late 1980s complaining of back and neck pain. The pain had a strong inflammatory pattern, associated with 40 minutes of morning stiffness and pain in both ankles. She had an episode of acute inflammatory symptoms that lasted for a week and she responded to a short course of NSAID. Aside from being a heavy smoker, she had a job that involved manual labour. On subsequent follow-up, her symptoms were only partially relieved with NSAID, eventually with complete loss of response over time. Her radiographies had been unremarkable, with no sacroiliitis and no syndesmophytes. She had the HLA-B27 haplotype and her erythrocyte sedimentation rate was elevated (C-reactive protein was not performed at that time). After 10 years of follow-up the patient developed radiographic damage: radiographic sacroiliitis (meeting the mNY criteria for AS) and syndesmophytes. Her symptoms had been controlled with opioids because she could no longer tolerate long-term high-dose NSAID. Her symptoms changed from predominantly inflammatory to mostly mechanical, caused by structural damage. This led to her taking early medical retirement at the age of 45.

REFLECTION ON THE CASE

Back in the 1980s when the patient described first presented, she did not meet the mNY criteria for AS and her disease would, at the most, be classified as 'undifferentiated' spondyloarthropathy. If the ESSG classification or Amor et al.[5] criteria were available and used, the patient would have been correctly classified as having SpA (without a specific phenotype) and if the ASAS criteria were applied she would have met the criteria for nr-axSpA. If MRI imaging was appreciated as the gold standard and used at the time when the patient presented, it would have certainly added important information regarding local inflammation (bone marrow oedema) in this patient with symptomatic nonradiographic axial disease on initial presentation. Even if the patient had been correctly classified, there would have still been important limitations at that time, including the lack of objective disease activity measures (e.g., BASDAI or ASDAS) and an objective treatment target and, as well as the lack of effective treatments besides NSAID.

In spite of current obstacles, there is optimism on the availability of more sensitive classification criteria, better imaging techniques, and treatments (such as bDMARD) that will enhance the possibilities of improving care.

TAKE-HOME MESSAGES

- Better classification criteria acknowledge the heterogeneity of spondylarthritis as a spectrum of disease and enable its early recognition.
- All forms of axial spondylarthritis, regardless of radiographic sacroiliitis, belong to the same continuum. This means all require prompt referral to a rheumatologist, a correct diagnosis, and early management.
- It is important to follow an objective treat-to-target approach in order to treat early, within the window of opportunity, minimising the risk of irreversible damage.
- Treat-to-target strategies should be tailored to patient preferences and comorbidities in order to avoid toxicity and increase compliance.

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Methotrexate and The Lung in Rheumatoid Arthritis

EDITOR'S PICK

The systemic nature of rheumatoid arthritis (RA) is exemplified by pulmonary fibrosis. Methotrexate (MTX), the most commonly used drug in RA is reviewed. It exerts its immunosuppressive effects by interfering with folate metabolism, adenosine signalling mechanisms, generation of reactive oxygen species, adhesion molecule expression, and alters cytokine profiles. Common side-effects include neurotoxicity, anaemia, and gastrointestinal discomfort, as well as MTX-induced pneumonitis (MTX-pn). RA patients can develop interstitial lung disease (ILD), which is similar to MTX-pn in that it occurs within 2 years of RA disease onset if not given optimal therapy. Here, Al Nokhatha et al. discuss the risk factors associated with MTX-pn and ILD and the treatment options such as rituximab, tocilizumab, abatacept, antifibrotics, and glucocorticoids. However, recent evidence shows increased risk of ILD worsening in patients treated with biodrugs. Activation of JAK2 kinase promotes fibrosis. I believe the time is now ripe to use JAK2 kinase inhibitors such as baricitinib early in RA rather than MTX or biologics to mitigate risks of ILD development.

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Abstract

Rheumatoid arthritis (RA) is a common systemic rheumatic disease. While the most visible manifestation of RA is articular involvement, it is a true systemic disease with the potential to affect multiple organs. Methotrexate (MTX) is the most commonly used medication to treat RA. MTX pneumonitis (MTX-pneu) is a rare disease entity reported in MTX users. It usually develops acutely or subacutely in the first year of treatment. MTX-pneu presents with cough, dyspnoea, and often fever. Pre-existing lung disease is a major risk factor and the clinical diagnosis is based on MTX exposure, symptoms, and laboratory and imaging findings. Treatment involves MTX cessation and high-dose glucocorticoids. Interstitial lung disease (ILD) is a common manifestation of RA with clinical RA-ILD affecting up to 10% of patients. RA-ILD tends to be a more indolent process than MTX-pneu and frequently develops over years but can also be acute. Similar to MTX-pneu, RA-ILD presents with cough, dyspnoea, and often fever. Risk factors include age, male sex, disease activity, seropositivity,

and smoking. Treatment is aimed at optimal control of RA disease and within this strategy there may be particular roles for rituximab, tocilizumab, and abatacept. Antifibrotics may also have a role. Given the distinct pathologies, the differentiation of these two entities is crucial. The treatment approach differs significantly and what is beneficial for one may be harmful for the other. In this paper, the authors discuss and contrast contemporary knowledge of MTX-pneu and RA-ILD.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder affecting 0.5–1.0% of the global population. While primarily seen as a condition affecting joints, it is more accurately a systemic inflammatory disease which can affect multiple organ systems including the lungs. Among the extra-articular manifestations, respiratory disease is the second most common cause of death after cardiovascular disease.[1] A large autopsy study of 1,246 RA cases from Japan corroborates the lung involvement, including interstitial lung disease (ILD), second to infection as the most common cause of death.[2]

Given the significant role of ILD as part of the natural history of RA, there has been much controversy over the role of methotrexate (MTX) as the anchor disease-modifying antirheumatic drug (DMARD). On one side of the debate is the idea that MTX may cause ILD in RA. On the other side, including the view of the authors, is that ILD or fibrosis in the expected usual interstitial pneumonia (UIP) pattern is a result of poorly controlled RA and the resultant active systemic inflammation. As to how uncontrolled chronic inflammation predisposes to lymphoproliferative disorders and amyloidosis, it is the authors' view that in the context of RA, poor disease control predisposes to RA-related interstitial lung disease (RA-ILD). As such, there is an association or correlation between MTX use and ILD, but there is a confounding variable, namely that most cases have underlying RA; a classic case of how correlation does not imply causation. There is also a historic channelling bias as patients with more severe RA were traditionally both more likely to develop RA-ILD and to be treated with MTX.[3,4]

A supported association between MTX and ILD first appeared in the literature over 30 years ago.[5] An important distinction to be made is what is meant by ILD and if it is present at baseline before treatment with MTX. In terms of MTX and lung injury, the most commonly reported manifestation is MTX-related pneumonitis (M-pneu) which can be difficult to distinguish clinically from underlying RA-ILD.[6] In short, this is where much confusion arises and why MTX and its putative role in the lung is misunderstood. MTX may very rarely cause drug-related pneumonitis but it also may have a protective effect against progressive RA-ILD, these being two distinct pathological entities. Elucidating the precise cause of respiratory symptoms in an RA patient may be difficult but it is crucial to guide treatment. A comparison of the features of MTX-pneu, RA-ILD, idiopathic pulmonary fibrosis (IPF), and *pneumocystis jiroveci* pneumonia (as an example of an atypical infection) is shown in Table 1. The aim of this manuscript is to review the current understanding of MTX-pneu and RA-ILD.

METHODS

A systematic literature search for relevant articles using PubMed, the Cochrane central register of controlled trials, and Embase was done. The search was performed with no date limits and last updated on 4th March 2020. The keywords 'Methotrexate' OR 'rheumatoid arthritis' AND ('lung' OR 'respiratory') were used. Reference lists of relevant articles were also reviewed.

METHOTREXATE PNEUMONITIS

Epidemiology

The prevalence of M-pneu as documented in the literature ranges anywhere from 0.3–11.6%, with the caveat that diagnostic criteria used for M-pneu are not consistent across studies.[7-10] A previous comprehensive literature review of 3,463 RA patients treated with MTX reported a 2% rate of some form of lung toxicity with only 15 cases (0.43%) of MTX-pneu.[11]

Table 1: Comparison of features of methotrexate-associated pneumonitis, RA-ILD, IPF, and PJP.

	Methotrexate-associated pneumonitis	Rheumatoid arthritis-associated interstitial lung disease	Idiopathic pulmonary fibrosis	Pneumocystis jiroveci pneumonia
Frequency in rheumatoid arthritis	0.3–11.6%	10.0%	By definition 0.0%, but 1.0% in general population	0.1–0.3%
Course	Acute or subacute onset and course	Insidious onset and course (can rarely be acute)	Insidious onset and course (can rarely be acute)	Acute or subacute onset and course
Clinical symptoms/ signs	Nonproductive cough Dyspnoea Fever Chills Malaise Chest pain	Nonproductive cough Exertional dyspnoea Fever Clubbing Bilateral basal crackles Rheumatic hand changes Rheumatic nodules	Nonproductive cough Exertional dyspnoea Gastro-oesophageal reflux Clubbing Bilateral basal crackles	Non-productive cough Exertional dyspnoea Fever Chest pain Chills Fatigue
Supportive investigations	BAL: lymphocytosis Serum levels of KL-6 and surfactant protein D PFT: restrictive pattern Exposure history to MTX and temporal history	Rheumatoid factor Anti-cyclic citrullinated peptide PFT: restrictive pattern	BAL: limited value, neutrophils used to exclude other causes PFT: restrictive pattern Exclusion of pulmonary fibrosis with known causes	Sputum/BAL polymerase chain reaction - *Pneumocystis jiroveci* Unexplained elevation in lactate dehydrogenase Serum levels of KL-6 and S-adenosylmethionine
High-resolution CT	Nonspecific interstitial pneumonia: scattered or diffuse ground-glass opacities in the early stage or basal fibrosis in the later stages Cryptogenic organising pneumonia: poorly defined nodular consolidations, centrilobular nodules, bronchiolitic or tree-in-bud changes and bronchial dilatation	Majority UIP Non-UIP pattern: non-fibrotic nonspecific interstitial pneumonia and cryptogenic organising pneumonia/ bronchiolitis obliterans organising pneumonia	UIP pattern: bibasilar reticular abnormalities or honeycombing with minimal ground glass opacities, with or without traction bronchiectasis	Diffuse areas of ground-glass opacities
Treatment	Figure 1	Figure 2	Antifibrotics: nintedanib pirfenidone	Trimethoprim/ sulfamethoxazole Alternatives: pentamadine, atovaquone, primaquine/ clindamycin ± Glucocorticoids

BAL: bronchoalveolar lavage; PFT: pulmonary function tests; UIP: usual interstitial pneumonia.

In an even more favourable review of seven trials and 1,630 patients without RA, but with diagnoses ranging from psoriasis; psoriatic arthritis; or inflammatory bowel disease, who were treated with either MTX or placebo, did not show a statistically significant increase in adverse respiratory events within 52 weeks of treatment and only one case of pneumonitis was identified in the MTX group.[12] This provides some evidence of the safety of MTX itself and may suggest that there are factors attributable to the inherent RA disease process which increase the risk for acute lung injury when subjected to MTX. Of particular interest, since 2001, there has been no reported cases of M-pneu across all randomised clinical trials of MTX in RA.[13] The recent CIRT trial of MTX enrolled 6,158 patients and reported 6 possible cases of pneumonitis in the MTX group compared to 1 case in the placebo group, but there was insufficient evidence to confirm that these cases were definite MTX-pneu.[14]

Clinical Presentation and Symptoms

While distinguishing between M-pneu and RA-ILD can be difficult given the overlap of clinical and histological features, M-pneu tends to have an acute or subacute course with a propensity for developing within the first year of treatment.[15-17] This reiterates the need to study the baseline respiratory function of RA patients in clinical studies prior to commencing DMARD. This would help to distinguish between the subsequent development of M-pneu or RA-ILD.

While the presentation may be nonspecific, the symptomatology of M-pneu typically may include fever, chills, malaise, nonproductive cough, dyspnoea, and chest pain. The presentation tends to be either acute with progressive symptoms over days, or subacute with an insidious onset over weeks.[18]

Mild blood eosinophilia has been noted in 25–40% of cases of subacute M-pneu by some authors and similarly a small case series demonstrated lymphopenia in the context of M-pneu, with a return to normal once lung function is restored.[6,7,19,20] These signs may not be reliable but can serve as a clue to the aetiology of lung involvement.

Pathogenesis

M-pneu is generally considered to be a hypersensitivity reaction. *In vitro* studies suggest that IL-8 plays a role in the pathogenesis and it is known that MTX can trigger IL-8 secretion within airway epithelial cells, with resultant increased levels found in both peripheral blood samples and bronchoalveolar lavage (BAL) samples.[21-23] To the best of the authors' knowledge, IL-8 inhibition for pneumonitis has not been used in clinical practice with pilot trials terminating early.

Risk Factors

Various risk factors for M-pneu have been identified but have not always been reliably replicated in other studies. These include age >60, diabetes, hypoalbuminaemia, previous DMARD exposure, chronic kidney disease, male sex, increased Health Assessment Questionnaire (HAQ) score, decreased pain Visual Analog Scale (VAS), and crucially, pre-existing lung disease.[24] In a case-control study intended to identify and investigate risk factors for M-pneu, pre-existing lung disease was found to confer increased risk with an odds ratio of 7.1 (95% confidence interval: 1.1–45.4).[25] Taking this into consideration, the most recent iteration of the British Society of Rheumatology's guidelines note that while not an absolute contraindication to traditional DMARD initiation, caution should be exercised in commencing treatment in those with poor respiratory reserve.[26] The concern being that these patients with poor baseline respiratory function (e.g., diffusing capacity for carbon monoxide <40%) are less able to tolerate any occurrence of drug-induced pneumonitis.

Haplotype and single nucleotide polymorphisms have not proven to be particularly useful on a global scale, with borderline significance for the latter.[27] Interestingly, there seems to be a relationship with increasing latitude and risk for M-pneu. Data from the Ministry of Health of New Zealand suggests that the risk or incidence ratio increases by 16% per degree of increasing latitude.[28] Whether this is reflective of a genetic predisposition, single nucleotide polymorphisms, environmental factors, or ultraviolet light exposure and vitamin D level much like the relationship between vitamin D and multiple sclerosis remains unclear.[29]

Investigations

A diagnosis of M-pneu is typically based on clinical and radiologic findings. While pulmonary function tests (PFT), BAL, or lung biopsy are useful, the latter, at least, may not be practical. BAL can be beneficial as it can be used to rule out infections secondary to immunosuppression. The characteristics of BAL in M-pneu have been well defined in the literature with a systematic review highlighting that the majority (89%) of BAL samples in M-pneu demonstrate lymphocytosis.[30] Furthermore, serum levels of KL-6 and surfactant protein D, both expressed by Type II pneumocytes in the lung, are increased in M-pneu and may have utility as novel biomarkers to aid diagnosis, with the caveat that both are increased in other forms of lung pathology including RA-ILD. Careful consideration is needed and relative change to pre-MTX baseline may be more useful than raw values.[31,32]

As elucidated earlier, invasive investigations are not always practical or indicated. However, a study comprising 44 patients with drug-induced lung injury did conclude that transbronchial lung biopsy was diagnostically helpful in 75% and, as such, may aid diagnosis in conjunction with clinical, laboratory, and radiographic findings.[33]

The predominant radiographic findings in M-pneu are typical of nonspecific interstitial pneumonia (NSIP) most commonly followed by cryptogenic organising pneumonia (COP)/bronchiolitis obliterans organising pneumonia.[34] The NSIP pattern is characterised by diffuse heterogeneous opacities on chest X-ray, scattered or diffuse ground-glass opacities in the early stage, or basal fibrosis in the later stages on CT. The less common COP pattern can be described as demonstrating bilateral scattered heterogeneous or homogeneous opacities with a peripheral distribution in the upper and lower lobes on chest X-ray and poorly defined nodular consolidations, centrilobular nodules, bronchiolitic or tree-in-bud changes, and bronchial dilatation on CT. Imaging findings in MTX-pneu have been reviewed in detail elsewhere.[35-38]

Diagnostic Criteria

Two proposed diagnostic criteria are those laid out by Searles et al. and those by Kremer et al.[6,39] The former has tended to be used most often, where six out of nine criteria must be met for a diagnosis of M-pneu. Baseline PFT abnormalities, such as low forced expiratory volume in 1 second, vital capacity, and diffusing capacity for carbon monoxide, may have prognostic roles and aid in identifying those at higher risk of developing M-pneu.[17] Previously, many authors felt that MTX should only be commenced in RA patients if they were believed to have sufficient respiratory reserve to survive M-pneu. However, recent literature would suggest that M-pneu is rarer than previously thought and, given the many proven benefits of MTX, a careful risk–benefit analysis should be made in this group.

Treatment

The treatment approach is summarised in Figure 1. Discontinuation of MTX is the clear first step in suspected M-pneu. Given that M-pneu is seen as a hypersensitivity reaction, steroids (either methylprednisolone or oral prednisolone) in high doses are often required. There are case reports of benefits from cyclophosphamide and tocilizumab.[40,41]

Prognosis

Once MTX is stopped, prognosis in M-pneu tends to be favourable with most recovering fully.[18] Three different studies have reported mortality ranging from 13% to as high as 30%.[6,9,18,42]

Rapid onset of M-pneu following initiation of MTX appears to be associated with poorer prognosis.[16]

RHEUMATOID ARTHRITIS INTERSTITIAL LUNG DISEASE

Epidemiology

ILD is an under-recognised extra-articular manifestation of RA. The prevalence of RA-ILD varies between studies. Clinical RA-ILD has been estimated to occur in approximately 8–10% of RA patients, with respiratory symptoms preceding articular symptoms in about 10–20% of cases.[3,43,44] A study of 140 RA patients by Bharadwaj et al.[45] corroborates this, demonstrating the presence of ILD in 9.29% of cases and highlighting that ILD is the most common extra-articular complication of RA. Studies from the UK including the ERAS/ERAN study and the BRILL study have reported a slightly lower prevalence of ILD (3–5%).[46,47]

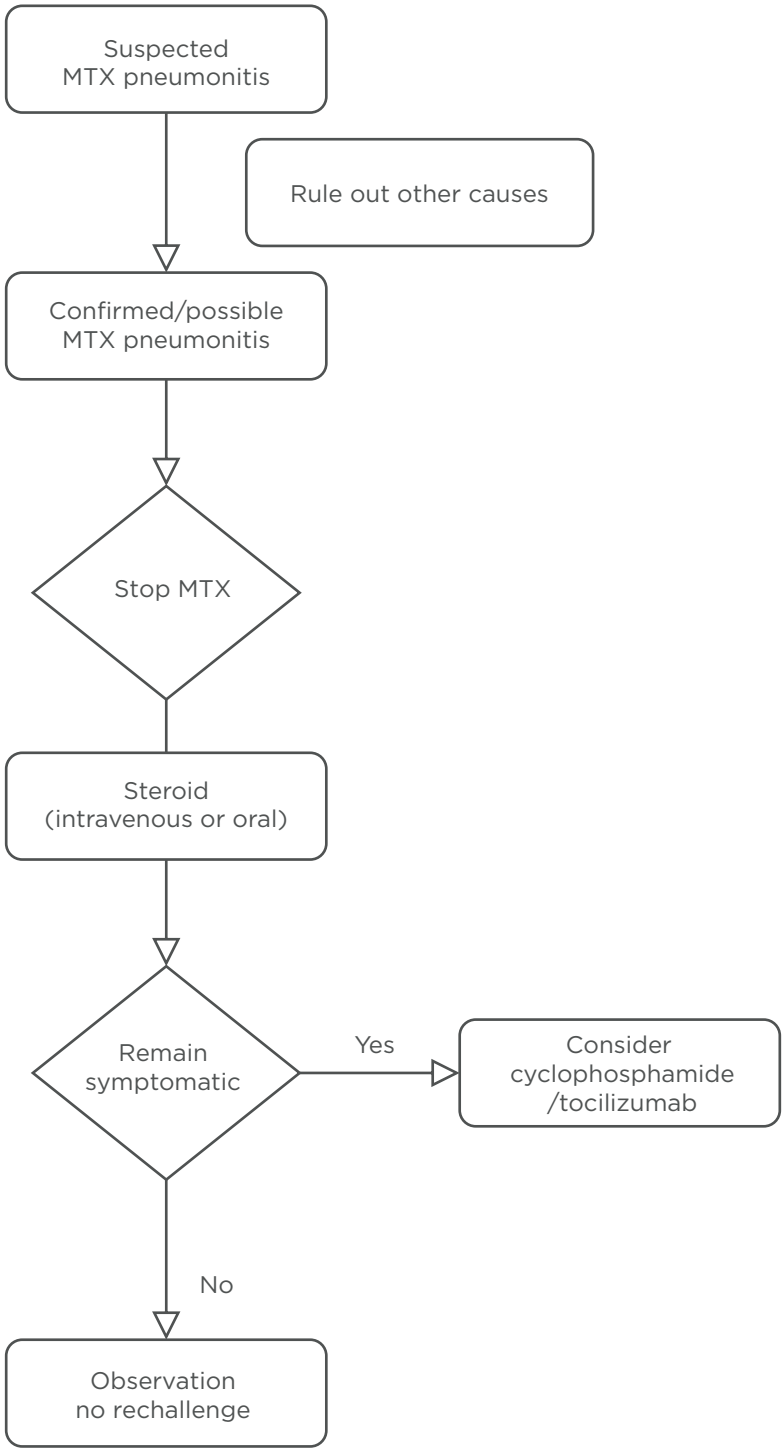

Figure 1: Management of methotrexate-associated pneumonitis.

MTX: methotrexate.

Subclinical RA-ILD as evaluated by high resolution CT (HRCT) has been identified in 19–67% of RA patients, while unselected lung biopsy identified evidence of ILD in 80% of patients.[48-50]

Clinical Presentation and Symptoms

The clinical symptoms of RA-ILD and M-pneu can be difficult to differentiate. RA-ILD, which can be asymptomatic for years, tends to develop insidiously over time in contrast to M-pneu which would more typically present acutely or

subacutely with dyspnoea, cough, and fever.[35] Traditional articular features of RA can limit mobility and exercise tolerance to the extent that exertional dyspnoea early in the course of RA-ILD is masked by this forced sedentary lifestyle. While subtle radiographic features may be present early in the disease process on HRCT, auscultatory findings may be absent initially but most cases will eventually develop fine bibasal crackles.[51] Radiographically, most will develop a UIP pattern often in conjunction with digital clubbing on clinical examination; a pattern very similar to that seen in IPF patients.[51] Imaging findings in RA-ILD have been reviewed in detail elsewhere.[35,36,52]

Pathogenesis and Risk Factors

While there is still much to be understood regarding the pathogenesis of RA-ILD, there is increasing evidence to suggest that the lung may be central in activating the pathological process of RA itself.[53-55]

Multiple risk factors for RA-ILD have been identified including older age, male sex, smoking, disease activity, elevated titres of specific autoimmune antibodies, ethnicity, and certain human leukocyte antigens.[3,55-57] In terms of biomarkers, a positive rheumatoid factor or anti-citrullinated peptide antibody are strongly associated with RA-ILD. Other novel biomarkers have emerged, with heat shock protein 90 detected in blood samples of RA-ILD patients as well as BAL samples.[58,59] Of particular significance is the gain-of-function *MUC5B* promoter variant rs35705950, which is strongly associated with ILD involvement, conferring an increased odds ratio of 3.1 in RA patients. The similarities between RA-ILD and IPF are striking. Both typically demonstrate a UIP radiographic pattern with clubbing, and the *MUC5B* variant is often involved in both, acting as the strongest predictor or known risk factor for IPF.[60,61]

THE ROLE OF METHOTREXATE IN RHEUMATOID ARTHRITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE

Much has been made of the association between MTX and RA-ILD over the past few decades. While there is an association with MTX and RA-ILD, it is now known to be coincidental and not causative, with the underlying inflammatory process driving ILD. In short, it is the disease and not the drug that causes RA-ILD.[62]

The seminal studies that explore the role of MTX in RA-ILD are the ERAN and ERAS studies which recruited 2,701 RA patients in the UK and Ireland to the trial with a follow-up period of up to 25 years.[46] In this multicentre prospective cohort trial, the diagnosis of ILD was according to standard practice with confirmatory evidence from standard investigations including PFT, chest X-ray, and HRCT. The authors compared the prevalence of RA-ILD in the MTX exposed and the non-MTX exposed groups. They demonstrated that in the MTX exposed group 97.5% (n=1,539) remained ILD free, whereas in the non-MTX exposed group 95.2% (n=1,061) remained ILD free. This is statistically significant and shows that there is no causation between MTX exposure and development of RA-ILD. Patients who developed ILD were, at RA onset, a mean 5.14 years older and mean baseline ESR score of 8.64 mm/hour higher than patients who did not develop ILD. Furthermore, ERAS and ERAN confirmed that higher age of RA onset, male sex, smoking, rheumatoid factor positivity, rheumatoid nodules, higher ESR, and longer time from first RA symptom to first outpatient department visit were independently associated with incident RA-ILD. The authors of the ERAN and ERAS study concluded that the overall prevalence of RA-ILD is 3.7%, in line with the UK BRILL network which reported 2–3% prevalence across its recruiting centres.[47] There was no association between MTX exposure and incident RA-ILD. On the contrary, MTX exposure was associated with significantly less RA-ILD and this would suggest a protective effect in delaying the onset of ILD.

Treatment

ILD management in systemic RA is still a challenge due to disease heterogeneity. Asymptomatic patients frequently do not require any specific treatment in comparison to progressive symptomatic patients or those with deteriorating PFT. Histologic subset, if known, can guide treatment approach. Nonfibrotic NSIP and COP/bronchiolitis obliterans organising pneumonia are more likely to have a positive treatment response in comparison to the UIP pattern. Most RA-ILD cases present with a UIP pattern raising the question as to the relative benefits of immunosuppressive versus antifibrotic treatment strategies.

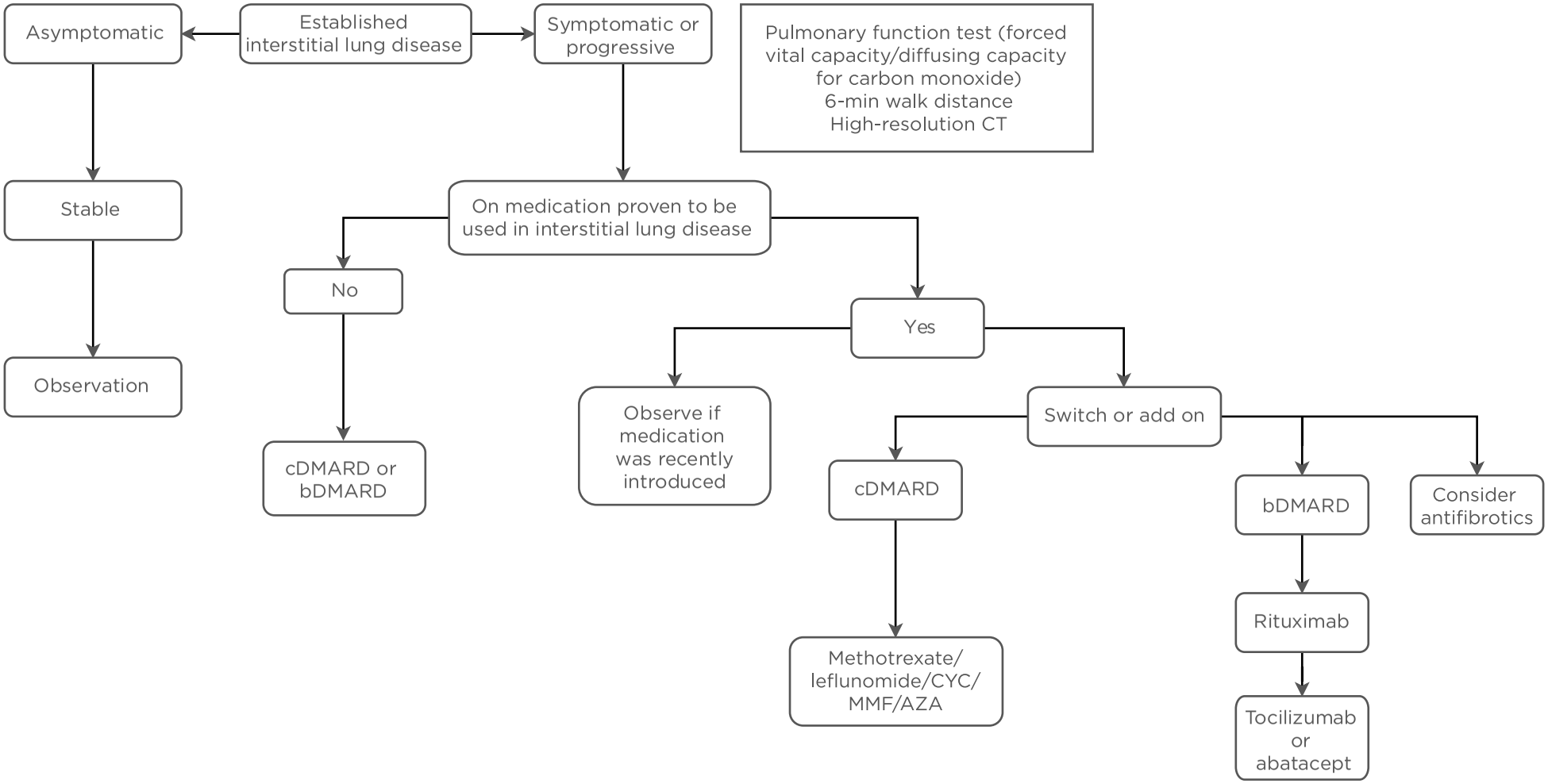

Figure 2: Management of rheumatoid arthritis-associated interstitial lung disease.

AZA: azathioprine; b: biologic; c: classical; CYC: cyclophosphamide; DMARD: disease-modifying antirheumatic drug; MMF: mycophenolate mofetil.

UIP pattern ILD in systemic rheumatic diseases may be more responsive to immunosuppression than IPF.

Given the overall excellent response of RA to DMARD, it is intuitive that the pulmonary component of the disease is also likely to be responsive to these treatments. The absence of any definitive evidence that RA-ILD is a predominantly immune-mediated inflammatory rather than fibrotic process, however, ensures that this remains controversial. The aim of treatment is to ensure complete overall rheumatoid disease control using whichever available agents to achieve this goal.[4,56] The rationale for this strategy is supported by the significant decline in RA-ILD as treatment options have advanced, and the improved articular outcomes achieved by the authors.[63] The treatment approach is summarised in Figure 2. The available medication options include glucocorticoids which remain the initial mainstay of therapy but, due to long-term adverse effects, steroid-sparing agents are generally introduced early in the disease course. MTX and leflunomide are important anchor agents in the treatment of RA joint disease. The best available evidence shows no sign of harm in RA-ILD and some evidence of benefit.[4,46,64,65] Among the biologic agents rituximab has shown particular promise and has demonstrated improved mortality compared to tumour necrosis factor-inhibitors (TNF-I).[66-68] An observational study of 56 patients with RA-ILD treated with rituximab showed that 16% improved and 52% remained stable following treatment.[69]

The preference for other biologics in the setting of RA-ILD is less certain. In addition to the study comparing rituximab and TNF-I, another literature review also showed an increased mortality with the use of TNF-I.[70] It remains unclear if TNF-I are harmful or if they are merely not as effective as some other biologics in treating RA-ILD. There are some preliminary supportive data for the use of abatacept or tocilizumab for RA-ILD.[40,71-74] The role of other agents traditionally used in other forms of connective tissue disease-associated ILD, including cyclophosphamide, mycophenolate mofetil, and azathioprine, is less certain.

The antifibrotic agents pirfenidone and particularly nintedanib have recently sparked interest in the treatment of ILD in the setting of systemic rheumatic disease, including RA, based on initial positive results in the setting of IPF.[75] Nintedanib has also demonstrated positive results in systemic sclerosis-related ILD.[76] Both antifibrotic agents have been shown to be effective in animal models of RA-ILD.[77] The INBUILD study of nintedanib demonstrated efficacy in fibrotic lung disease other than IPF.[78] While subgroup analyses were too small to demonstrate statistical significance, patients with RA-ILD appeared to respond similarly to the overall cohort.[79] The absolute benefits of these anti-fibrotic agents in terms of lung function appear modest, and must be balanced against the high frequency of adverse events, particularly gastrointestinal issues.[78]

CONCLUSION

The ultimate choice of therapeutic strategy in RA-ILD relies on the individual patient's symptoms, comorbidities, and balancing adverse events. A collaborative multidisciplinary team approach between rheumatologists and respiratory physicians is important to ensure optimal care.

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Bone Health in Rheumatoid Arthritis: What Can Studies of Bone Microarchitecture Tell Us?

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Abstract

Introduction: Rheumatoid arthritis (RA) is associated with changes in skeletal health, including increased risk of fracture. This study used a novel technique, high-resolution quantitative CT (HRpQCT), to assess bone microarchitecture in patients with RA.

Methods: There were 59 patients (female: 41; male: 18) with RA recruited. They underwent dual energy X-ray absorptiometry and HRpQCT of the radius and tibia. The questionnaire information included age, sex, BMI, disease duration, comorbidities, medication use, smoking and alcohol consumption, rheumatoid factor (RF) or cyclic citrullinated peptide (CCP) status, and disease activity. HRpQCT results were compared with published estimated age and sex-specific values.

Results: There were 55 patients (female: 39; male: 16) who had either radial or tibial scans available. The mean age was 55.8 (standard deviation [SD]: 12.6) years and median disease duration was 11.4 years (interquartile range [IQR]: 6.3–19.4). Mean BMI was 27.2 (SD: 5.8). Forty-nine (90.7%) participants were RF or CCP positive, with disease severity ranked as severe in 33 (61.1%) patients and moderate in 20 (37.0%). Fifteen participants (27.8%) had previously taken steroids and 47 (85.5%) were receiving tumour necrosis factor inhibitor (TNF-i) medication. Radial trabecular number and density were lower than expected, and trabecular separation was greater than expected ($p<0.05$), though tibial results were similar ($p<0.10$ for trabecular number and separation). No difference in cortical values reached statistical significance in this sample. Previous use of steroids was associated with greater radial periosteal circumference ($p<0.05$, adjusted for sex) and use of TNF-i agents was associated with lower radial total and trabecular area ($p<0.05$, adjusted for sex).

Conclusion: Trabecular bone microarchitecture differences were observed among patients with RA. Further studies with larger numbers of participants are needed.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory arthritis[1-3] characterised by synovial inflammation and hyperplasia,[3,4] autoantibody production,[2-4] and destruction of cartilage and bone.[2,3,5,6] It is relatively common, with an estimated prevalence of 0.5–1.0% in the population, and often affects the small joints of the hands and feet.[4] The disease is known to cause bone erosions[2,3,6] and periarticular osteopenia.[1,6] A common and important comorbidity is a generalised reduction in bone mineral density (BMD),[2,3,5-8] with patients with RA having an estimated two-fold increase in the frequency of osteoporosis compared to healthy controls.[5,8] Multiple studies using dual energy X-ray absorptiometry (DXA) have demonstrated reductions in BMD in patients with RA at sites including the hip[8-12] and the lumbar spine.[10-12] This loss of bone is thought to occur early in the disease[5,10,12,13] and is associated with higher disease activity,[10,12,13] increased functional disability,[8-11,13] and longer disease duration.[10,11,13] Additionally, RA is associated with an increased risk of skeletal fractures of the hip[14-17] and the vertebrae.[16,18,19]

Corticosteroids have been commonly used in patients with RA to control inflammation with great clinical efficacy,[20] but they are also known to have negative effects on bones by increasing osteoblast apoptosis and osteoclast activity.[21,22] It was traditionally thought that the reduced BMD and increased fracture risk observed in patients with RA were due in large part to steroid use in this cohort. However, whilst there is evidence that steroids do reduce BMD[7-10,21,23,24] and increase fracture risk in RA,[15-17,21] there is also evidence that their use has only a minimal effect on BMD.[11,19,22] Additionally, with the development of biologic therapies, steroids are used less frequently and for shorter durations in patients with RA.[20] One might speculate that bone health would be better in cohorts of RA treated with current therapeutic agents because of their strong anti-inflammatory effects and good clinical efficacy. However, a recent study that utilised the UK Biobank to evaluate this found that a diagnosis of RA remains associated with poorer bone health, as assessed by heel ultrasound, and an increased frequency of falls and fractures.[24] It was also found that corticosteroids and conventional disease-modifying therapy, but not biologic therapy, were associated with lower epithelial BMD.[24]

Bone strength is not purely determined by BMD[19,25] but also by bone quality, which is affected by bone remodelling, microarchitecture, and mineralisation of the bone matrix,[25,26] and may contribute to risk of fracture.[25] There is growing evidence that RA may increase skeletal fracture risk by impairing bone quality in a manner independent from BMD,[5,19,24] potentially by altering the bone remodelling process.[26] High-resolution peripheral quantitative CT (HRpQCT) is a useful tool to assess bone microarchitecture and can separate cortical and trabecular bone at distal sites, and give true measurement of compartmental volumetric bone density.[7,26,27] Its use in the diagnosis or assessment of erosive disease progression in inflammatory arthritis has been well studied,[26] but far fewer data are available that consider its utility in the assessment of generalised skeletal health. Three previous studies that have used this technology for this purpose have all focussed on the radius.[28-30] They reported that both trabecular and cortical radial bone were severely affected in male and female patients with RA, with volumetric BMD in both compartments being reduced. In this study, the authors set out to study bone health in a group of patients with RA recruited from general rheumatology clinics, and specifically to extend sites of interest to include the tibia, which can also be assessed by HRpQCT. The following variables derived by HRpQCT at the radius and tibia in patients with RA were considered: bone area; trabecular number, density, separation, and thickness; and cortical density and thickness.

MATERIALS AND METHODS

Fifty-nine patients with RA were recruited to the study at the Osteoporosis Centre in Southampton, UK. Participants were approached in general rheumatology clinics, with many contacted through the Southampton Biologics

service. They completed a self-reported questionnaire on age, sex, height, weight, time since RA diagnosis, comorbidities, medication use (including tumour necrosis factor inhibitors [TNF-i] and steroids), and smoking and alcohol consumption. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) status was recorded, as well as the physician and patient assessment of disease activity from patient records.

Participants underwent DXA of the total hip and lumbar spine using a Hologic Discovery™ machine (Hologic Inc, Bedford, Massachusetts, USA). HRpQCT scans of the distal radius and tibia were obtained using XtremeCT-I, (Scanco Medical, Bassersdorf, Switzerland). A stack of 110 parallel HRpQCT slices were acquired with an isotropic voxel size of 82 µm. The standard evaluation and cortical porosity scripts were run to obtain estimates of various indices of bone health, including cortical and trabecular BMD and trabecular thickness. Fifty-six of the participants had radial scans, of which 25 were excluded because of excessive motion artefact (Grade 4 or 5 on the standard grade system), leaving 31 patients with useable radial scans available. Fifty-seven of the participants had tibial scans, of which four were excluded because of excessive motion artefact, leaving 53 patients with useable tibial scans available. In total, 55 participants had either radial or tibial scans available. Results were compared with estimated age and sex-specific values calculated from the formulae in the paper by Dalzell et al.[31] Ethical approval was obtained from Hertfordshire REC (reference 13/EE/0215).

STATISTICAL ANALYSIS

Descriptive statistics for continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were expressed as frequency (N) and percentage. Wilcoxon signed-ranks tests were used to compare the HRpQCT values with estimated age and sex-specific values calculated from the formulae in the paper by Dalzell et al.[31] The HRpQCT outcomes were transformed to Fisher–Yates z-scores using the Fisher–Yates rank-based normal transformation to normalise the data. Linear regression analyses were used to examine the associations between patient characteristics and the HRpQCT outcomes (as z-scores) after adjusting for sex. Analyses were performed using Stata version 14 (StataCorp, College Station, Texas, USA).

RESULTS

The characteristics of the study population are shown in Table 1. The mean age of the 55 participants was 55.8 (SD: 12.6) with 39 participants (70.9%) being female. Median disease duration was 11.4 years (IQR: 6.3–19.4). Mean BMI was 27.2 (SD: 5.8). Forty-nine (90.7%) participants were RF or CCP positive, with disease severity ranked as severe in 33 (61.1%) patients and moderate in 20 (37.0%). Fifteen participants (27.8%) had previously taken steroids and 47 patients (85.5%) had previously taken TNF-i. The median (IQR) T and Z scores at the lumbar spine were -0.8 (-1.8, 0.3) and -0.1 (-0.8, 1.3) respectively; corresponding figures at the total hip were -0.8 (-1.4, 0.2) and -0.2 (-0.7, -0.6), respectively. Three patients were taking anti-osteoporosis medication at the time of scanning; adjusting for taking this medication did not affect the results. The characteristics of the 59 participants were considered, comparing those with (n=31) and those without (n=28) useable radial scans; there were no statistically significant differences between them. A similar comparison of those with (n=53) and without (n=6) useable tibial scans again showed no statistically significant differences.

Usable radial scans were obtained from 31 of the 55 recruited patients. Expected values were calculated from age and sex using published means.[31] The p-values were calculated by comparing the actual values with the expected values using Wilcoxon signed-ranks tests. Compared to expected values, patients with RA had significantly lower trabecular number (median: 1.82 mm^{-1} versus 1.93 mm^{-1}, respectively; p=0.014) and significantly lower trabecular density (median: 140 mg/cm^3 versus 148 mg/cm^3, respectively; p=0.048) (Table 2). They also had significantly lower trabecular separation (median: 0.486 versus 0.488, respectively; p=0.046). Steroid-use was associated with greater radial periosteal circumference (regression coefficient: 0.561 z-score; p=0.03) and use of biologic agents was associated with lower radial total area (regression coefficient: -0.585 z-score; p=0.02) and lower trabecular area (regression coefficient: -0.581 z-score; p=0.03), after adjustment for sex.

Table 1: Participants' characteristics.

Participant characteristic	Mean (SD)
Age at time of study (years)	55.8 (12.6)
Height (m)	1.65 (0.08)
Weight (kg)	74.6 (18.5)
BMI (kg/m²)	27.2 (5.8)
	Median (IQR)
Disease duration (years)	11.4 (6.3–19.4)
Patient global assessment of disease activity	3.5 (0.9–5.1)
Physician global assessment of disease activity	2.5 (1.4–4.2)
Alcohol consumption (units per week)	2.0 (0.0–4.0)
	N (%)
Sex	
Male	16 (29.1)
Female	39 (70.9)
Ethnicity	
English/Welsh/Scottish/Northern Irish/British	48 (98.0)
Any other Caucasian background	1 (2.0)
RF or CCP positive	49 (90.7)
Disease severity	
Mild	1 (1.9)
Moderate	20 (37.0)
Severe	33 (61.1)
Smoking status	
Never smoked	26 (48.1)
Ex-smoker	18 (33.3)
Current smoker	10 (18.5)
Ever had a fracture	22 (40.0)
Number of comorbidities	
0	31 (56.4)
1	12 (21.8)
2	7 (12.7)
≥3	5 (9.1)
Previously taken steroids	15 (27.8)
Previously taken biologics	47 (85.5)
Have periods (females only)	
No	25 (64.1)
Yes	14 (35.9)
Previously taken HRT (females only)	
No	25 (69.4)
Previous use	9 (25.0)
Current use	2 (5.6)

CCP: cyclic citrullinated peptide; HRT: hormone replacement therapy; IQR: interquartile range; RF: rheumatoid factor; SD: standard deviation.

Table 2: Comparison of mean high-resolution quantitative CT (HRpQCT) parameters from participants with expected values.

HRpQCT parameter		Actual value		Expected value*		
	N	Median	IQR	Median	IQR	p-value
Radius						
Total area (mm^2)	31	301	225–426	283	255– 392	0.308
Trabecular number (mm^{-1})	31	1.82	1.35–2.07	1.93	1.87– 2.11	0.014
Trabecular density (mg/cm^3)	31	140	93–177	148	141–176	0.048
Trabecular thickness (mm)	31	0.065	0.057–0.073	0.061	0.057 – 0.085	0.953
Trabecular separation	31	0.486	0.412–0.689	0.488	0.407 – 0.516	0.046
Cortical bone density (mg/cm^3)	31	829	768–905	854	806– 916	0.112
Cortical thickness (mm)	31	0.670	0.560–0.820	0.736	0.643 – 0.858	0.468
Tibia						
Total area (mm^2)	52	702	627–834	714	685– 899	0.044
Trabecular number (mm^{-1})	53	1.85	1.59–2.18	1.88	1.85– 2.07	0.161
Trabecular density (mg/cm^3)	53	153	128–186	168	158– 185	0.088
Trabecular thickness (mm)	53	0.073	0.63–0.083	0.070	0.063–0.073	0.023
Trabecular separation	53	0.459	0.385–0.555	0.484	0.427–0.505	0.328
Cortical bone density (mg/cm^3)	53	832	780–902	851	820–877	0.753
Cortical thickness (mm)	53	0.940	0.760–1.1210	1.047	0.904 – 1.092	0.493

HRpQCT: high-resolution quantitative computed tomography; IQR: interquartile range.
**Expected values are the age- and sex-specific values calculated from the formulae in the paper by Dalzell et al.[31]*

Radial cortical bone density and cortical thickness were reduced in patients with RA relative to expected values, but differences did not reach significance.

Figure 1 shows a typical tibial scan. Usable tibial scans were obtained from 53 of the 55 recruited patients. Tibial total area was significantly decreased in patients with RA compared to expected values (median: 702 mm^2 versus 714 mm^2, respectively; p=0.044) and tibial trabecular thickness was significantly increased (median: 0.073 mm versus 0.070 mm, respectively; p=0.023). While similar trends towards reduced volumetric BMD in cortical and trabecular compartments were seen at the tibia, and trabecular separation was lower, these effects were less noticeable than at the radius and failed to reach statistical significance. No association between tibial indices and previously taking steroids or biologics could be found in this study population.

DISCUSSION

The results have shown significant differences in trabecular bone parameters between patients with RA and healthy controls that were more pronounced at the radius. These results are in line with previous studies using HRpQCT, which have also shown reduced radial trabecular density,[28-30] reduced trabecular number,[30] and increased trabecular network inhomogeneity[28-30] in patients with RA, relative to controls. Reductions in trabecular number have been shown to be related to disease duration,[30] indicating ongoing loss of trabecular bone over time. There is evidence from previous HRpQCT studies that healthy patients who subsequently present with fractures have lower radial trabecular density, number, and thickness,[32,33] and higher trabecular separation[32] compared to nonfractured age-matched controls, suggesting an important contribution of bone microarchitecture to fracture risk.

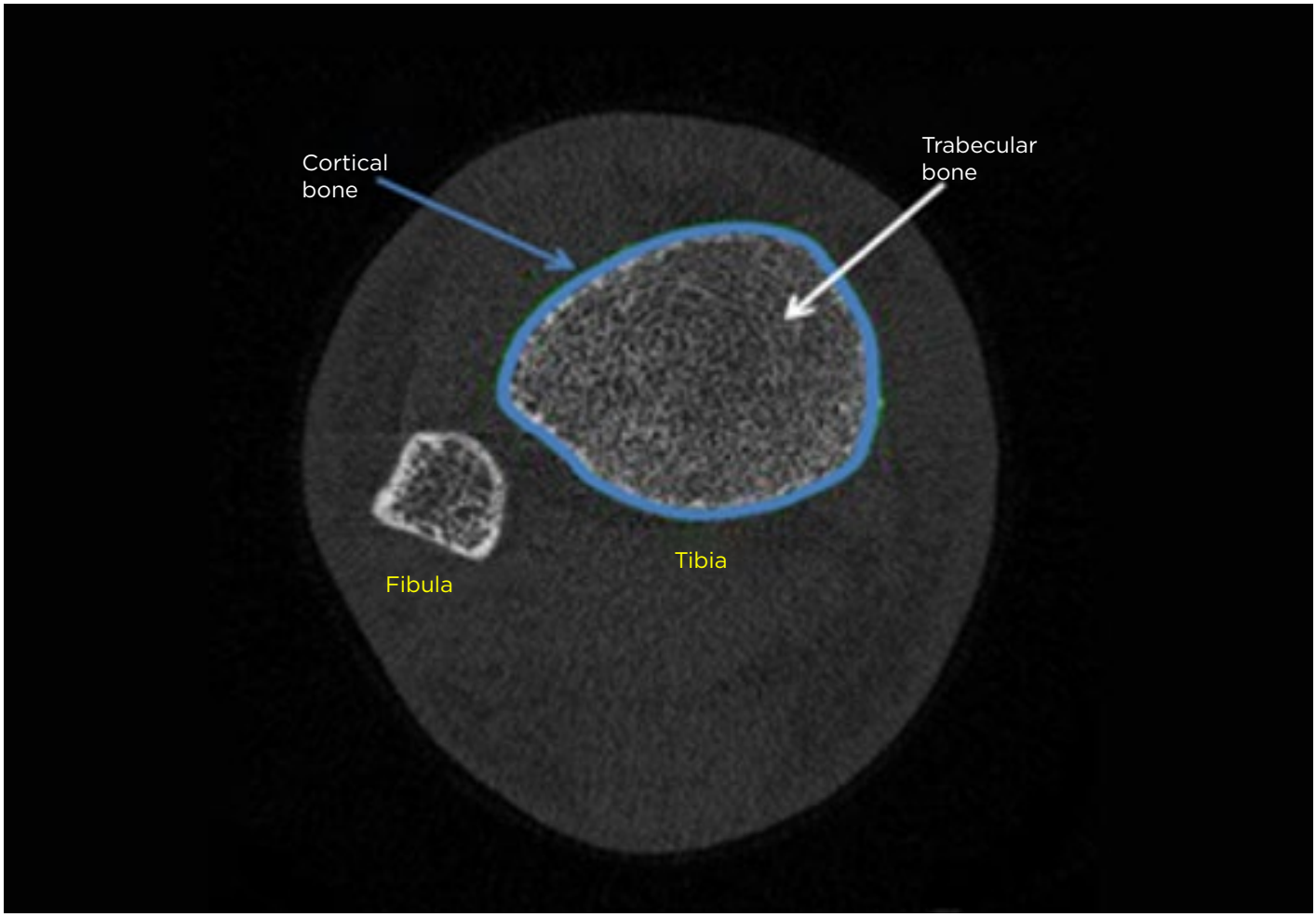

Figure 1: Typical tibial high-resolution quantitative CT (HRpQCT) scan.

As patients with RA in this cohort demonstrated similar alterations in their radial microarchitecture, it is possible that these alterations in bone quality could contribute to the increased fracture risk seen in this study. Few studies have considered whether wrist fracture is particularly increased in patients with RA, but despite an increased risk relative to controls, other sites (e.g., hip, pelvis, humerus) seem more vulnerable.[17] Whilst there is evidence that both trabecular and bone are deficient in patients with RA,[28-30] any differences in cortical microarchitecture did not reach significance in this patient population.

The bone loss that occurs in RA is known to be related to inflammation.[5,6] T cells stimulate the production of inflammatory cytokines such as TNF-α and IL-1 from monocytes, macrophages, and synovial fibroblasts,[2-4] which in turn have the ability to induce expression and release of the cytokine receptor activator of NF-κB ligand (RANKL).[1,2,4] RANKL binds to its receptor RANK and mediates bone resorption by osteoclasts.[1,2,4,5] Additionally, IL-1 and TNF-α are able to directly upregulate osteoclast bone-resorbing capacity and stimulate the development of osteoclast precursor cells into mature osteoclasts.[1,4] Several studies have shown patients with RA to have increased bone resorption markers compared to normal controls,[7,34] which suggests they develop an imbalance between bone formation and resorption,[1] leading to an overall loss of bone. Zhu et al.[29] found a correlation between volumetric density; microstructure indices; and disease activity, severity, and levels of inflammatory cytokines, suggesting that inflammation may contribute to the observed impairments in bone quality as well as reducing BMD.

Whilst corticosteroids have been shown to reduce BMD[7-10,21,23,24] and to increase fracture risk in RA,[7,15,21,24] their anti-inflammatory properties have a beneficial effect on bone which may outweigh the negative effects.[22] This leads to

an overall improvement of BMD in patients with RA treated with steroids,[6,10,11,23,35] particularly in those who have severe disease with high levels of inflammation. Some studies have identified that RA itself can reduce BMD[9] or increase the risk of fracture in a manner that is partially independent from the increased risk incurred by steroid use.[6,15,16] Additionally, there is evidence that the bone loss and increased fracture risk seen with steroids is reversible after discontinuation of therapy.[21] Current guidelines suggest that steroids still have a place in RA management as an adjunct to conventional disease-modifying therapies, but that their use should be limited to the lowest possible dose for the shortest possible duration when treating disease flares or switching from one disease-modifying drug to another.[20] In this study population, only 15 patients (27.8%) had ever taken steroids, therefore it was not possible to comment on any potential effect they may have had on bone microarchitecture. There is evidence that steroid use causes reduced cortical and trabecular BMD[21,36] and that high doses may cause cortical thinning,[30] but other studies have shown that exposure to steroids does not significantly affect bone density or microstructure.[28,29] The finding of increased periosteal circumference in patients who have received steroids as part of their disease management could reflect an 'aging phenotype' of bone, represented by an enlarged periosteal circumference to compensate for endosteal bone loss. This would be interesting to study in larger samples of patients who have received these drugs.

The efficacy of biologic therapies such as TNF-i and anti-IL-1 drugs supports the pathogenic role of these cytokines in the disease process,[1,4] but the effect of such treatment on bone health remains uncertain. In this study population, most patients (85.5%) had taken TNF-i. Based on the knowledge that inflammation stimulates bone resorption, it is reasonable to hypothesise that tight control of inflammation with medication should reduce bone damage in RA patients.[2,25] Improvement in BMD[37] or stabilisation and reduction of bone loss has been recorded with biologic treatments that target specific cytokines, but results have been inconsistent.[36-41] The effect of such treatments is thought to be more pronounced on generalised bone loss rather than local damage, as evidenced by the continuing hand bone loss seen in several studies.[38,41] However, some biologic therapies have been shown to reduce the progression of bone erosions.[36] There is also evidence that anti-TNF treatment may suppress bone resorption in RA.[37] Kim et al.[42] showed that biologic therapy does appear to reduce fracture risk compared to methotrexate or other nonbiological disease-modifying drugs, but further studies on fracture rate post-initiation of biologic therapies are needed.[36] In the UK Biobank data there was no statistically significant association between biologic therapy and epithelial BMD, falls, or fracture for participants with RA.[24] Of note, in a longitudinal study by Guler–Yuksel et al.,[35] no difference in BMD loss was observed between patients managed with four different treatment strategies (including corticosteroids and anti-TNF medications). Additionally, in a study by Kocijan et al.,[30] no specific associations between biological agents and bone microarchitecture could be identified. Both of these factors suggest that the direct impact of a specific treatment modality on bone strength may be less important than its effectiveness at suppressing inflammation and reducing the related damage to bone.[30,35] In this study a high proportion of patients recruited were receiving biologic therapies, limiting the opportunity to study relationships between disease activity and bone health. However, despite this, and even in this relatively small sample size, trabecular alteration in the bones of patients with RA was observed.

Another mechanism that might lead to an association between RA and poor bone health is lack of weight-bearing physical activity because of the active disease.[6] In this population, patients with RA had increased tibial trabecular thickness compared to normal controls, which was an unexpected finding. That there was a less apparent effect of RA at the tibia, the weight-bearing site of interest, or as assessed by total hip BMD, suggests this factor may be less contributory than systemic inflammation. In a study by Boutroy et al.,[27] women with osteoporosis had reduced trabecular number and thickness and increased trabecular separation compared to women with osteopenia, which is similar to the radial findings from patients with RA in this study. Additionally, women with osteopenia and fractures had reduced radial trabecular density and more heterogeneous trabecular distribution than nonfractured women with osteopenia,[27] again

suggesting this cohort may have impairments in their bone quality which put them at increased risk of fracture. Previous studies have shown a link between trabecular parameters of the radius and skeletal fracture that is relatively independent of DXA-measured bone density,[32] highlighting the value of HRpQCT for assessing bone parameters where it is available, especially as forearm BMD is rarely performed in clinical practice. As the majority of fractures in postmenopausal women occur in those who have an osteopenia rather than an osteoporotic range of BMD,[43] it is highly likely that other factors contribute to fracture risk.[27] As patients with RA may have impairments in their bone quality that are independent from BMD,[19,25,26] there are recommendations that there should be a lower threshold for starting anti-osteoporotic treatment in this cohort to protect them from fracture.[25] Additionally, patients with RA may be at increased risk of falling because of pain, functional impairment, and physical disability,[24] which again may impact on their fracture risk independently of bone quality.[7,44]

Despite advances in biologic therapies and the treatment of RA, there is still evidence that these patients are still at increased risk of fracture compared to healthy controls.[17,45] This could be because of the fact that even optimum treatment does not completely suppress inflammation in RA,[2] or because of alterations in bone microarchitecture that occur independently from BMD changes as a result of the disease. There is also evidence that the rates of skeletal fracture in patients with RA are increasing despite new developments in treatment, which may be because of the aging population.[46] All of these factors further highlight the importance of being aware of bone health in patients with RA and initiating therapies to protect against skeletal fracture.[25] There is evidence from several studies that low proportions of patients with RA who meet the criteria for anti-osteoporotic therapy are actually taking the medication,[23,35] and poor adherence to such therapies is well recognised.[25]

There are, of course, many limitations to this pragmatic study and more work in larger patient populations is very important, particularly to include patients with early RA, and those with very well controlled disease. The population studied was relatively small and the authors did not use their own controls, but compared the results from the cohort with the expected values from a different UK population. A validated tool, the physician global scale,[47] was used to assess disease activity. However, other recognised scores such as the Disease Activity Score-28 (DAS28) were not available in this dataset. Additionally, many of the patient characteristics were self-reported, and may have been subject to bias. Steroid and biologic use were considered as binary variables and therefore the effect of dose or length of usage could not be analysed. However, the results serve to highlight the skeletal effects of RA and encourage consideration of volumetric BMD in studies where HRpQCT are being undertaken. They also emphasise the importance of recognising bone quality alongside BMD when considering skeletal health in this population.

CONCLUSION

This study adds to the evidence that patients with RA have alterations in their radial trabecular bone microarchitecture compared to healthy controls, which may contribute to the increased fracture risk seen in this population. Clinicians should be aware of the direct effect of RA on bone microarchitecture, even in patients who are optimally treated using biologic therapies, and should consider implementing strategies to protect bone, such as the use of anti-resorptive medications. In an ageing population, the prevalence of osteoporosis and rate of fragility fractures in patients with RA is likely to increase, and there may be a limitation to the reduction in fracture risk that can be achieved through improving BMD alone. Further studies in larger study samples are indicated, as are studies looking at skeletal fracture as the endpoint.

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Systemic Sclerosis

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Abstract

Systemic sclerosis (SSc) is a complex autoimmune rheumatic disease that is characterised by widespread skin and internal organ fibrosis, immune system dysregulation, and vasculopathy. The disease carries a significant burden of pain and disability that is potentially life-limiting because of major internal organ-based complications. Early diagnosis is vital and key investigations include the detection of SSc-associated autoantibodies and nailfold capillaroscopic abnormalities. Patients should be managed by a dedicated, specialist, multidisciplinary team. There is now a range of effective treatments available for many of the complications associated with the disease. Autologous haematopoietic stem cell transplantation may benefit a small subset of patients with very poor prognosis SSc. Important advances have been made in understanding the aetiopathogenesis of SSc, which is driving clinical trials of new therapeutic approaches. The purpose of this review is to provide a clinically focussed description of the relevant aetiopathogenesis, clinical expression of disease, approach to the assessment and treatment of SSc, and highlight the recent advances and future challenges associated with this complex disease.

INTRODUCTION

Systemic sclerosis (SSc) is a complex autoimmune rheumatic disease that is characterised by widespread skin (scleroderma) and internal organ fibrosis, immune system dysregulation, and vascular alterations.[1-4] SSc is a rare rheumatological condition (prevalence: ~20 per million) and is more common in females than males (~7:1).[5] The purpose of this review is to provide a clinically focussed description of the aetiopathogenesis, clinical expression of disease, approach to the assessment and treatment of SSc, and highlight the recent advances and future challenges associated with this complex disease.

PATHOGENESIS

The pathogenesis of SSc is complex and includes vascular alterations (vasculopathy), immune system dysregulation, and aberrant tissue fibrosis.[1-3] It is believed that key interactions between vascular changes and early immunological alterations are central to the generation of the SSc-phenotype.[1,2] Vasculopathy is thought to occur early in the course of the disease including defective/reduced/uncontrolled mechanisms of vascular repair.[1,2] However, the trigger of this early putative vascular injury remains elusive. Ineffective neoangiogenesis, which can be assessed using nailfold capillaroscopy, is clearly apparent in SSc. A key vascular alteration in SSc is a critical imbalance between factors promoting vasoconstriction (e.g., endothelin) and vasodilation (e.g., nitric oxide).[1] Local ischaemia (hypoxia) contributes to promote a profibrotic phenotype. Immune (both innate and adaptive) system activation is seen in SSc.[1,2] For example, many patients have evidence of SSc-associated antibodies and there is a rich perivascular infiltrate seen in the skin of patients with early diffuse cutaneous SSc. The close relationship between cancer and anti-RNA polymerase III antibodies further highlights the role of immunological abnormalities in SSc.[2,6] In these patients, there is a link between cancer-related autoantigen (i.e., mutated RNA polymerase III) recognition and an autoimmune response.[7] *Type I interferon* and interferon-inducible genes have been strongly implicated in the pathogenesis of SSc.[8,9] Subsequent to vascular injury and immune disturbances, activated fibroblasts result in the excess deposition of extracellular matrix, which includes collagen, resulting in organ dysfunction and tissue fibrosis.[1,2] Fibroblast transition to myofibroblasts is believed to be a cardinal step in the ultimate stage of SSc pathogenesis.[2] Although genetic abnormalities are the strongest risk factor for the development of SSc, a family history of the disease is rare.[10] Susceptibility genes identified so far belong in a very large majority to immune mediators, further highlighting the immune component of the disease. Recent research has highlighted the key role of epigenetic modifications in genetically susceptible individuals; for example, those that link inflammatory and fibrotic pathways.[2,11]

CLINICAL FEATURES OF SYSTEMIC SCLEROSIS

One of the great challenges in the management of patients with SSc is the significant clinical heterogeneity of disease within the SSc-spectrum of disorders. Skin thickening (i.e., scleroderma) can occur as an isolated phenomenon (e.g., morphoea) or as part of a systemic, multiorgan, autoimmune connective tissue disease (e.g., SSc). However, characteristic SSc-like organ involvement can also occur in the absence of skin involvement ('scleroderma sine scleroderma'), which may represent about 10% of SSc patients.

Skin

Scleroderma (Figure 1) is a cardinal feature of SSc-spectrum disorders. The distribution of skin disease allows classification of patients into two major subsets: limited and diffuse cutaneous SSc (Table 1).[12] Skin involvement in limited compared to diffuse disease does not extend proximal to the elbows/knees, or involve the chest/abdominal wall. Sclerodactyly refers to scleroderma of the digits. The sine scleroderma subset may resemble the limited cutaneous type, in that internal organ manifestations are the major determinant of outcome. Disease subtype has important prognostic implications including internal organ involvement (Table 1). In early SSc disease the fingers often have a puffy appearance.[13] Later in the course of the disease, the skin may atrophy; however, patients can be left with permanent joint contractures. Calcinosis (subcutaneous and intradermal calcium deposition) commonly affects 20–40% of patients with SSc, and is often subclinical (Figure 1).[14]

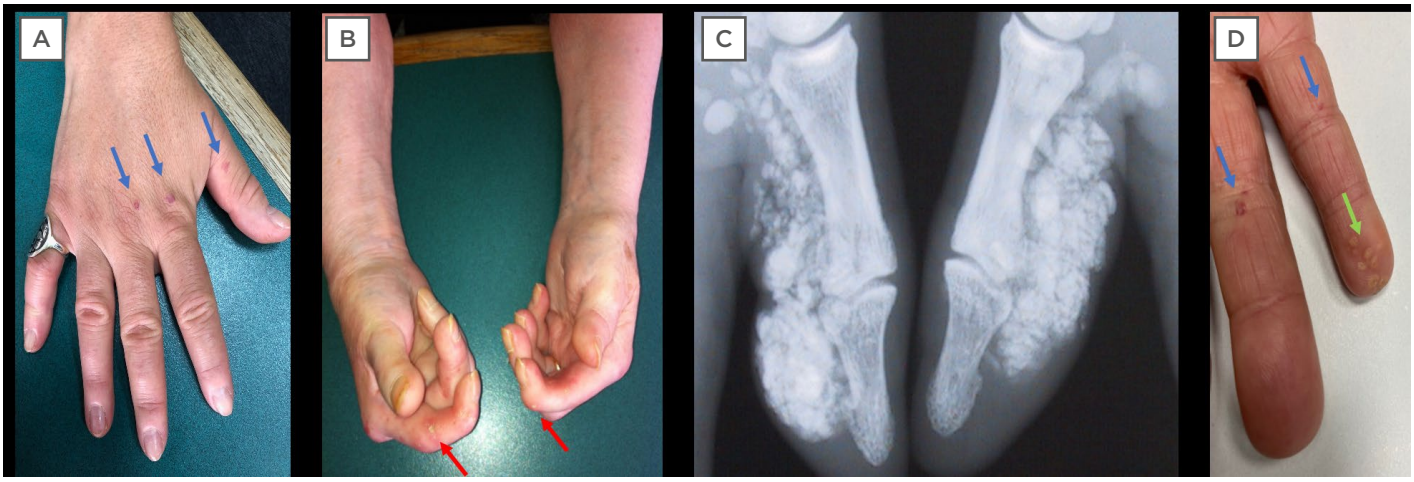

Figure 1: Cutaneous manifestations of systemic sclerosis.

A) Sclerodactyly and telangiectasia (blue arrows); **B)** digital pitting scars (red arrows) and hand contractures; **C)** radiographic calcinosis; and **D)** visible calcinosis (green arrows) and telangiectasia (blue arrows).

Table 1: Disease subsets in systemic sclerosis.

	Limited cutaneous systemic sclerosis	**Diffuse cutaneous systemic sclerosis**
Raynaud's phenomenon	Raynaud's phenomenon for many years before skin thickening	Recent onset of Raynaud's phenomenon in close proximity (before or after) skin thickening
Skin involvement	Hands, forearms, feet and below the level of the knees, and face and neck	As per limited cutaneous systemic sclerosis but also proximal upper and lower limbs and trunk
Organ involvement	Late onset of pulmonary arterial hypertension	Early cardiac, lung, gastrointestinal, and kidney involvement
Other features	Telangiectasia	Tendon friction rubs
Autoantibodies	Anti-centromere	Anti-Scl-70 (anti-topoisomerase), anti-RNA polymerase III

Adapted from LeRoy et al.[9]

However, calcinosis can cause significant pain from ulceration through the skin, superadded infection, and local pressure effects.[15] Telangiectasia (superficial dilated cutaneous) blood vessels can be associated with significant anxiety and distress from body image dissatisfaction (Figure 1).

Digital vasculopathy

Almost all patients with SSc experience events of Raynaud's phenomenon. Raynaud's typically affects the fingers and toes and is provoked by cold temperatures and or emotions/stress. Stereotypical colour changes (pathophysiological mechanisms in parentheses) are initial pallor (vasospasm), followed by cyanosis (sequestration of deoxygenated blood), and finally, hyperaemia

(reperfusion).[16] However, not all colour changes are reported by individuals during Raynaud's phenomenon.[16] Patients may also experience other symptoms such as numbness and tingling. Unlike patients with primary (idiopathic) Raynaud's phenomenon, patients with SSc can develop persistent ischaemic tissue loss.[17] Digital (finger and toe) ulcers are common in patients with SSc, with half of patients reporting a history of ulceration.[18,19] Digital ulcers often occur early in the course of the disease; 75% will experience within the first 5 years after their diagnosis, and are associated with a more severe disease course, including internal organ involvement.[18,20] Ulcers are often exceptionally painful and significantly impact upon hand function and quality of life, including affecting the patient's ability to carry out their chosen occupation.[21,22] Digital ulcers may be infected, in particular by *Staphylococcus aureus*, and can potentially progress to osteomyelitis.[23] Patients with SSc can also develop critical digital ischaemia (gangrene), which is a medical emergency and requires prompt assessment.[24] The peripheral pulses should be assessed early in patients with critical digital vascular disease as proximal large vessel disease could potentially be amenable to therapeutic intervention.[24]

Cardiorespiratory

Involvement of the entire cardiovascular system can occur in patients with SSc including, but not limited to, inflammatory/ischaemic/fibrotic cardiac disease and abnormalities of the conduction system.[25] An increased risk of macrovascular disease has also been reported in patients with SSc[26] but it may not always relate to classical atherosclerosis and SSc vessel remodelling, which primarily affects small vessels but sometimes also targets larger ones. Respiratory complications such as interstitial lung disease (Figure 2) and pulmonary hypertension are now the leading causes of death in SSc.[27] Evidence of Interstitial lung disease is present in half of patients when high-resolution CT (HRCT) is systematically performed and approximately one third develop progressive interstitial lung disease.[28-30] Risk factors include, but are not limited to, baseline lung involvement on HRCT, older age, male sex, presence of anti-Scl-70 (anti-topoisomerase) antibodies, and absence of anti-centromere antibodies.[29,30]

Gastrointestinal

The entire length of the gastrointestinal tract can be affected and this is almost universally seen in patients with SSc.[31] Reduced oral aperture, impaired upper limb function, and low mood can result in reduced oral intake. Gastroesophageal reflux disease is very common, along with swallowing difficulties and motility issues in the large bowel. Small bowel bacterial overgrowth can result in significant abdominal symptoms including bloating, distension, and diarrhoea. Gastric antral vascular ectasia, otherwise known as 'watermelon stomach' because of the striking visual appearance on endoscopy, can result in significant blood loss from the gastrointestinal tract.[31] Fecal incontinence is under-recognised, though reported by patients, and can result in significant distress and reduced quality of life. Hepatobiliary involvement can occur, including primary biliary cirrhosis which has been reported to occur in around 2% of patients with SSc.[31,32]

Renal

The scleroderma renal crisis is a medical emergency. Patients typically present with features of a hypertensive emergency.[33] Investigations typically reveal acute kidney injury and possible features of microangiopathic haemolytic anaemia. Risk factors for scleroderma renal crisis include early disease (<3 years duration), diffuse cutaneous SSc, anti-RNA polymerase III antibody, corticosteroid exposure (usually >15 mg/day), and tendon friction rubs.[33] This was previously the leading cause of death in SSc but is now usually a survivable complication because of the introduction of treatment with angiotensin-converting enzyme (ACE) inhibitors. Renal outcome is variable; some patients may require life-long renal replacement therapy, but around half of those requiring renal replacement therapy eventually no longer require dialysis. Recovery can occur for several years post renal crisis and ~40% of patients may recover sufficient renal function to no longer require renal replacement therapy.[34]

Musculoskeletal

Widespread involvement of the musculoskeletal system can occur in patients with SSc. Joint pains and stiffness are common and often multifactorial from skin tightness/sclerosis and

finger contractures. Patients can develop both inflammatory (i.e., rheumatoid-like) and non-inflammatory (i.e., degenerative/osteoarthritic) arthritis. Inflammatory muscle disease (myositis) can develop in patients with SSc and typically affects the proximal musculature. Bilateral carpal tunnel syndrome can occur early in the disease course of patients with diffuse cutaneous SSc. This is a high contributor to disability in SSc patients. Acro-osteolysis refers to bony resorption of the terminal digital tufts and is well-recognised in SSc.

Non-fatal morbidity

SSc carries a significant burden of non-lethal morbidity. Fatigue is common, often multifactorial, and difficult to treat, akin to many rheumatological conditions. Pruritus can be marked in patients with early diffuse cutaneous disease. Low mood or depression and sexual dysfunction are not uncommon in patients and should be actively considered by clinicians.[35,36]

DIAGNOSIS OF SYSTEMIC SCLEROSIS

There is no single diagnostic test for SSc. The diagnosis of SSc is usually based on the individual clinical features and from the results of targeted investigations such as SSc-associated autoantibodies and nailfold capillaroscopy. For the general physician, the diagnosis of SSc is very unlikely in the absence of Raynaud's phenomenon and distal skin involvement (e.g., sclerodactyly). However, there are caveats to this generalisation. The 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) SSc classification criteria are a helpful reference tool for assessing patients with possible SSc.[37] Involvement of skin proximal to metacarpophalangeal joints is usually diagnostic of SSc; however, it is important for the clinician to be aware of a number of important scleroderma mimics. Raynaud's phenomenon can occur soon (up to 1 year) after the onset of skin sclerosis in patients with diffuse cutaneous SSc.[12] Furthermore, very early diagnosis of SSc can be established in patients with Raynaud's phenomenon, puffy fingers, and positive antinuclear antibodies, and is confirmed by the presence of SSc-associated autoantibodies and/or capillaroscopic abnormalities.[38] In addition, patients with mixed connective tissue disease can display many features of SSc along with others of rheumatoid arthritis, myositis, and systemic lupus erythematous.[39] The majority of classification criteria require the presence of antibodies directed toward ribonucleoprotein (RNP) to make the diagnosis of mixed connective tissue disease.[39]

Systemic Sclerosis Mimics

There are a broad range conditions which can mimic many of the features of SSc. These include inflammatory or autoimmune diseases (e.g., eosinophilic fasciitis, graft versus host disease, nephrogenic systemic fibrosis, scleroedema, scleromyxoedema, diabetic cheiroarthropathy, amyloidosis, and carcinoid syndrome), drug-induced (e.g., aniline-contaminated rapeseed oil [toxic oil syndrome] and L-tryptophan [eosinophilia-myalgia syndrome]), and occupational exposures (e.g., epoxy resins, polyvinyl chloride, radiation fibrosis, and silica).[4,37] Furthermore, a number of genetic conditions can mimic SSc, such as stiff skin syndrome and Werner's syndrome, and can occur as the result of a paraneoplastic phenomenon.[4,37]

Investigations

The choice of investigations is based upon the clinical presentation. However, many clinicians perform extensive baseline investigations (e.g., HRCT of the thorax to investigate the presence of interstitial lung disease) as these could have important prognostic, and potentially treatment, implications. Patients with SSc require regular cardiopulmonary screening (usually on a yearly basis) with pulmonary function testing with or without conducting a transthoracic echocardiogram to assess for evidence of pulmonary hypertension, interstitial lung disease, and/or if the patient becomes symptomatic during follow-up.[40]

Autoantibodies

Autoantibodies, especially those that are SSc-specific, are very helpful tools which strongly inform the diagnosis and disease subset of SSc, and have important prognostic implications such as the likely pattern of internal organ involvement. The antinuclear antibody (ANA) test is positive in the majority (~95%) of patients with SSc.[41] Furthermore, specific SSc-antibodies targeting a wide range of nuclear and cytoplasmic proteins

can often be detected including, but not limited to, centromere proteins, topoisomerase 1, and RNA polymerases I-III.[42] ANA testing and many antibodies (e.g., anti-centromere) are typically routinely available in hospital laboratories. However, some are currently only available within research settings, such as anti-EIF2B antibodies.[42] Various autoantibodies can be observed in patients with overlap syndromes including anti-PM-Scl antibodies (myositis), anti-U1-RNP (myositis and/or systemic lupus erythematous), and anti-SS-A/Ro60 and anti-SS-B/Ro52 antibodies.[42] Rarely, SSc-spectrum disorders can also occur in the presence of anti-synthetase (e.g., anti-Jo-1), typically seen in patients with myositis.[42]

Nailfold capillaroscopy

Nailfold capillaroscopy allows examination of the microcirculation *in situ*. Low magnification (~x10) devices include the handheld dermatoscope, stereomicroscope, and ophthalmoscope.[43,44] High magnification (~x200–600) by videocapillaroscopy is considered the gold standard. Low magnification capillaroscopy allows for a broad, widefield view of the nailfold area and assessment of whether the capillaries are generally normal or abnormal. Normal capillaries have a regular, homogenous, hairpin-like appearance and are evenly distributed. This is reassuring in patients presenting with Raynaud's phenomenon. Conversely, in SSc and other related disorders there is progressive capillary enlargement (including 'giant' capillaries), microhaemorrhages, capillary loss/vascularity, and ineffective neoangiogenesis.[45] Such alterations can be seen early (years) before the clinical onset of SSc (e.g., skin sclerosis) and therefore is an important investigation to help make the early diagnosis of SSc. Similar capillaroscopic alterations can also be seen in dermatomyositis (e.g., ramified or 'bushy' capillaries).

Other specialist investigations

Infrared thermography (using a thermal camera) is used to measure skin blood flow and can be used to distinguish between primary and secondary Raynaud's phenomenon.[42] Functional/dynamic vascular assessment can be made through incorporation of cooling and heating challenges. At present, thermography is not widely available outside specialist centres because of the high cost of the equipment, but low-cost mobile devices may allow greater access in the future. Other investigations are dependent on the prevailing clinical picture. For example, cardiac MRI is used for suspected primary SSc heart disease and differentiation of fibrotic or inflammatory damages, as well as breath testing, often using glucose or lactulose as the substrate, for small bowel bacterial overgrowth.

MANAGEMENT

General principles

All patients with SSc should be managed as part of a specialist multidisciplinary team, including colleagues from specialist rheumatology nursing and allied health care professionals such as physiotherapists and podiatrists.[46] Patients are increasingly using internet-based information to learn more about their condition and to inform healthcare decisions and should be directed towards appropriate sources of information.[47] Patients are often managed under joint/shared care with local rheumatologists. Colleagues from general (internal) medicine are often involved in the care of patients with SSc including during acute episodes of hospitalisation and/or internal organ-based specialists such as respiratory medicine for lung involvement. Surgical intervention is sometimes required, including vascular and orthopaedic surgery. Patients with SSc can become critically unwell including from progression of their organ-based complications and infection/sepsis; the latter of which especially occurs if they are receiving high doses of immunosuppressive medication.[48]

Pharmacological Management of Systemic Sclerosis

There are a number of effective drug therapy treatments which are used in the management of patients with SSc. Mirroring the complexity of the SSc pathogenesis, broadly speaking (because there is overlap) drug treatments can be generally divided into three groups: vascular-acting, immunosuppressive/immunomodulatory, and anti-fibrotic. Access to treatments may vary between countries, for example because of local reimbursement policies.

Vascular-acting therapies

Vascular-acting (vasodilatory or vasoactive) therapies are central to the management of SSc. Vasodilatory/vasoactive therapies are used in the management of Raynaud's phenomenon and digital ulcers.[17] In addition to general, including lifestyle, measures such as keeping warm and stopping smoking, the majority of patients with SSc require pharmacological management for digital vascular disease. These include calcium channel blockers (e.g., nifedipine); in addition, clinicians are increasingly using phosphodiesterase-Type 5 (PDE5) inhibitors (e.g., sildenafil) earlier in the treatment of Raynaud's phenomenon, especially in SSc.[17] Other drug treatments include losartan, ACE inhibitors, and fluoxetine, the latter of which is useful in patients prone to vasodilatory side-effects.[17] The endothelin receptor antagonist bosentan is licensed in the UK and Europe for the prevention of digital ulcers in patients with severe/recurrent disease ulcer, but it does not impact on ulcer healing.[49] Many pharmacological treatments such as PDE5 inhibitors and endothelin receptor antagonists are also used in the treatment of pulmonary hypertension. In pulmonary hypertension, sequential or initial combination therapy is superior to monotherapy, offering improved survival.[50] Drugs can be used to target the endothelin (e.g., ambrisentan and macitentan), prostacyclin (e.g., selexipag and iloprost/epoprostenol), and nitric oxide (e.g., sildenafil and tadalafil) pathways.[51] ACE inhibitors are the first-line pharmacological treatment for the scleroderma renal crisis.[33]

Immunosuppressive/Immunomodulatory

Immunosuppressive agents (e.g., disease modifying anti-rheumatic drugs [DMARD]) that are used in other rheumatological conditions are sometimes also used in the management of SSc. Patients with early diffuse cutaneous SSc should be offered immunosuppressive treatment (e.g., methotrexate or mycophenolate mofetil) or more intensive therapy (e.g., intravenous cyclophosphamide).[52] Oral drug therapies are usually first-line treatment, with cyclophosphamide offered by some healthcare professionals in patients who are refractory and/or with serious internal organ-based complications such as myocarditis. Mycophenolate mofetil has been shown to be as efficacious as cyclophosphamide for the treatment of SSc-interstitial lung disease and is better tolerated by patients.[53] However, for patients who are refractory there is an increasing use of biologics, including rituximab and abatacept,[54,55] thanks to preliminary data obtained in patients with SSc and the huge experience of the community regarding their use in rheumatological-related diseases such as rheumatoid arthritis and lupus. Moreover, Phase II-III trials that showed a good safety profile despite not reaching the point of efficacy on primary outcome measures has meant that tocilizumab or abatacept may be offered in refractory patients with an inflammatory profile, in early disease, and with musculoskeletal involvement.

Autologous haemopoietic stem cell transplantation is a powerful potential treatment option in highly selected patients who are at high risk of severe/fatal disease progression.[56,57] Although significant improvement/stabilisation in skin and lung disease can be seen this should not be considered as a cure. Furthermore, there is a notable risk of treatment-related mortality (5–10% according to procedures) which is significantly higher in patients with cardiorespiratory involvement. Therefore, patients undergo extensive cardiorespiratory investigation during transplantation workup. Certain inflammatory complications (e.g., myositis) can benefit from treatment with oral steroid therapy. However, patients need to be closely monitored because of the potentially promoting scleroderma renal crisis.[58]

Anti-fibrotic

Therapeutic molecular targets of SSc-interstitial lung disease are being actively researched and anti-fibrotic therapies used for the treatment of idiopathic lung fibrosis are also being investigated in SSc.[59,60] Nintedanib was found in a recent Phase III trial to significantly reduce the annual rate of lung function decline (force vital capacity), leading to its worldwide licencing for the treatment of SSc-associated interstitial lung disease.[61] The optimal use of the drug still needs to be defined; however, the preliminary data suggest that overt disease, defined by >10% of interstitial lung disease on HRCT, may be appropriate. Moreover, the combination of

nintedanib and mycophenolate showed a good safety profile and may represent the most potent regimen to preserve lung function.

Future treatment options and challenges

Increasing understanding of the pathogenesis of SSc has driven the recent flurry of clinical trials for drug therapies for SSc.[62,63] However, demonstration of treatment efficacy of drug therapies is a significant challenge. Future studies need to consider the heterogeneity of the disease and important aspects of study design, such as patient selection and the incorporation of novel endpoints of treatment efficacy.[64-66]

CONCLUSION

SSc is a complex, multiorgan disease which has a high burden of patient morbidity and can be life-limiting. Great advancements have been made in understanding the aetiopathogenesis of SSc. There are a range of effective treatments for many of the internal organ-based complications. Demonstration of treatment efficacy in such a heterogeneous disease is very challenging and future clinical trials will need to address this. Patients with SSc should be managed by a specialist multidisciplinary team, including colleagues from general medicine and organ-based specialists who understand the possible complexities of the disease.

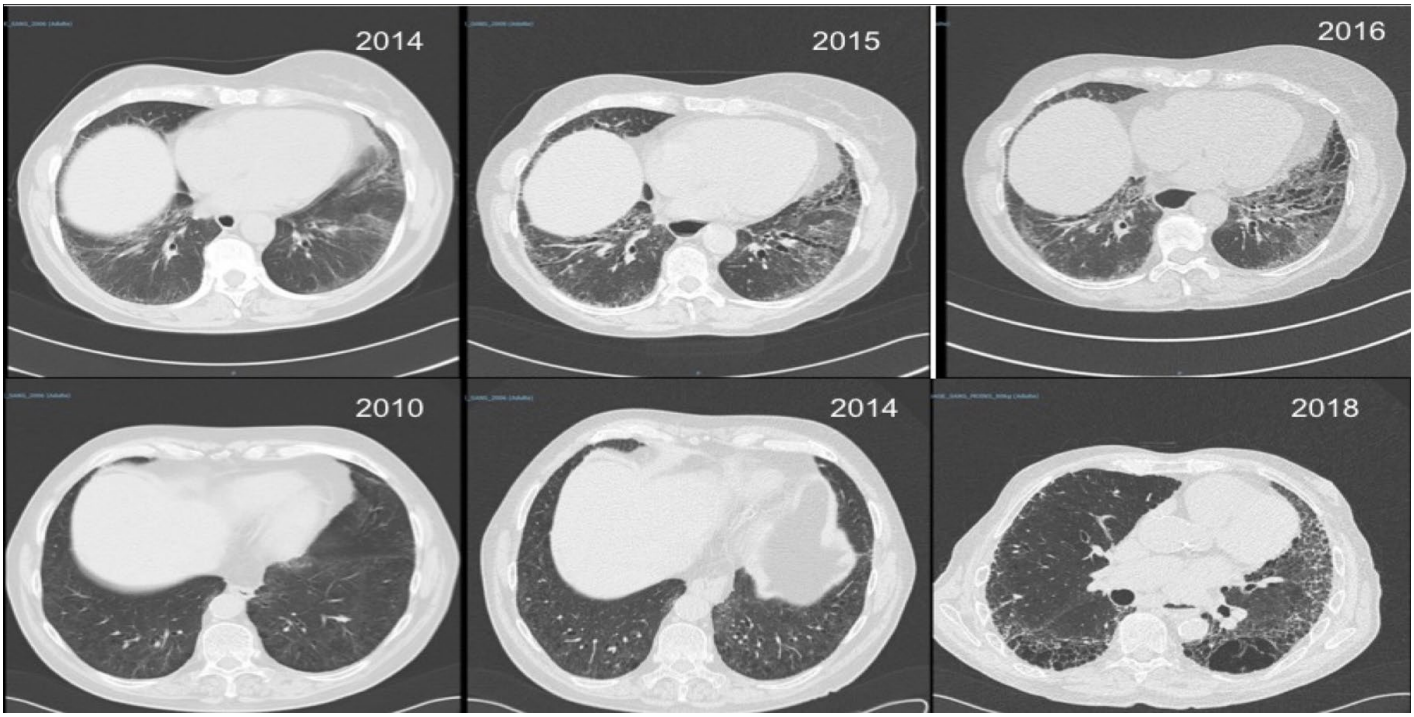

Figure 2: Interstitial lung disease in systemic sclerosis.

Two patients with systemic sclerosis and rapidly (top row) and slowly (bottom row) progressive interstitial lung disease.

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Using Audiometry to Track Atherosclerosis: Measuring a Beneficial Effect of Methotrexate in Rheumatoid Arthritis

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Abstract

Objectives: To correlate audiometry with atherosclerosis. Presbycusis is associated with age and atherosclerosis; a strong correlation might present opportunities to use audiometry to track atherosclerosis disease.

Design: The authors tested 87 elderly patients with rheumatoid arthritis (age range: 80–101 years; median: 86 years) with a history of methotrexate use for over 20 years. After 50 years of age, hearing loss begins slowly and by the age of 90, the majority of the general population require hearing aids. In the 87 elderly participants, however, hearing was remarkably preserved.

Results: The observed cohort of 87 individuals showed better hearing than predicted compared to audiometry historically documented in the elderly ($p<0.001$). The patients tested one to two decades younger than expected on audiometry and 44% of patients qualified for hearing aids instead of the expected 80%, based on age.

Conclusion: The known reduction in atherosclerosis with methotrexate use in rheumatoid arthritis may account for this observed preservation of hearing.[1,2] As hearing and atherosclerosis are related, the authors further postulated that routine audiometry may provide a cost-effective screening tool for other populations in future atherosclerosis studies.

INTRODUCTION

In the past 20 years, many studies have evaluated the relationship of systemic inflammation with atherosclerosis and coronary artery disease.[3] Immune cells are prominent in early atherosclerotic lesions; cytokines further accelerate the arterial lesions, and inflammation activates clotting of platelets, all leading to myocardial infarction and stroke. Macrophages play a key role in arterial plaque and this macrophage activation can be modified by methotrexate. Hundreds of publications in the past decade have shown that treatment of the underlying inflammatory

condition in rheumatoid arthritis significantly improved cardiovascular outcomes by reducing atherosclerotic disease.[4-8] In a 25-year multicentre prospective study of 5,626 patients with rheumatoid arthritis, methotrexate was associated with a 70% reduction in mortality.[1] Further prospective studies have demonstrated an additional 23% reduction of cardiovascular risk when methotrexate was utilised along with a biologic disease-modifying antirheumatic drug.[9] Control of inflammation, therefore, reduced atherosclerotic disease.[10]

There are many known causes of hearing loss and the single strongest aetiology is atherosclerosis. Presbycusis, hearing loss, has been shown to be largely secondary to atherosclerotic vascular disease and is well described.[11-13] Hearing acuity decreases with age and correlates strongly with the atherosclerotic small vessel disease in ageing.[14] Audiometry measurement is objective, readily available, inexpensive, and reproducible. In most studies of atherosclerosis in clinical trials today, the primary outcome is a change in a radiologic measurement such as carotid intima media thickness over 5 years, and secondary outcomes include nonfatal myocardial infarction, nonfatal stroke, coronary artery bypass grafting, percutaneous coronary intervention, peripheral atherosclerotic arterial disease–related amputation, peripheral atherosclerotic arterial disease revascularisation, and death due to vascular disease. Unfortunately, these outcome measures require long duration and expenses, include end-of-life measures, and do not easily allow for a continuum of measurement for disease progression.

Using audiometry as a potential secondary outcome and surrogate measure to track small vessel atherosclerosis is a logical extension of the authors' understanding of the pathophysiology and offers an objective, repeatable low-cost measurement. Furthermore, it is not dependent on local culture or language. Clinical trials with interventions to prevent atherosclerosis could then potentially be monitored by audiometry in a continuous time course as a potentially useful secondary outcome.

This study evaluated a population of elderly patients with rheumatoid arthritis at high risk of atherosclerotic disease due to ongoing systemic inflammation.[15] Rheumatoid arthritis populations have a 2-fold increased incidence of atherosclerosis compared to the normal population. Untreated rheumatoid arthritis is associated with increased mortality due to accelerated coronary artery and cerebrovascular atherosclerosis. The authors performed audiometry in a high-risk elderly population with rheumatoid arthritis (age range: 80–101 years old) who had been on continuous methotrexate for over 20 years. Significant presbycusis was expected in this group of individuals aged over 80 years old, but hearing was remarkably preserved so this prompted cross-sectional measurement of hearing in an observational study. For this group at high risk of atherosclerosis, because of rheumatoid arthritis with an underlying systemic inflammatory process, the authors hypothesised that that long-term methotrexate administration would be associated with both a low prevalence of atherosclerosis and a low level of hearing loss measured by audiometry. Rheumatoid arthritis does not cause hearing loss; the authors chose this cohort to study because rheumatoid arthritis has marked inflammation. Since chronic inflammation causes atherosclerosis and atherosclerosis causes hearing loss, treatment of chronic inflammation could result in less atherosclerosis and less hearing loss. In time, it followed that audiometry may prove to be a valuable, cost-effective marker to follow atherosclerosis.

METHODS

Conventional audiometry was performed on AMBCO 2500 equipment (AMBCO Electronics, Tustin, California, USA), in a single booth using the modified Hughson-Westlake procedure specified by the International Organization for Standardization (ISO) 8253-1:2010 Acoustics — Audiometric test method. The same equipment was utilised on each subject and the testing was performed by the same technician. Results were recorded for each ear at 250, 500, 1,000, 2,000, 4,000, and 8,000 hertz (Hz). Data was also analysed by quintile. Age, sex, language, socioeconomic status, education, medical history, tobacco use, concomitant medication, and vocation were recorded; additionally, all subjects had a physical and ear exam.

To evaluate proof of concept, this was a cross-sectional observation trial. There were 87

elderly individuals with rheumatoid arthritis enrolled sequentially, 15 were male and 72 were female. All subjects met the American College of Rheumatology (ACR) criteria for rheumatoid arthritis and were treated with methotrexate at time of disease onset. All subjects met the criteria for clinical remission, defined as Disease Activity Score-28 for Rheumatoid Arthritis with ESR (DAS28-ESR) <2.6, which accounts for solo methotrexate use for decades. Other activity measures such as Clinical Disease Activity Index (CDAI), Simple Disease Activity Index (SDAI), and Routine Assessment of Patient Index Data (RAPID) were not in use in the 1990s. Since these patients began methotrexate in the 1990s with good control of disease, other disease-modifying antirheumatic drug use or biologic use in later years was a rare event. Participants were excluded if there was any history of trauma to the ear, vocations with known damage to hearing, prior damage from ear infection or recurrent sinus infection, allergic rhinitis requiring current therapy, Ménière's disease, chronic vertigo, chronic tinnitus, prior temporal–mandibular joint surgery, ototoxic medication use, or neurosurgery. There were three subjects who had hearing aids at baseline enrollment and the other 84 subjects stated they had never been advised to get a hearing aid nor felt a need for one. The need for hearing enhancement was based on reference criteria defined by the Ventry and Weinstein criteria (>40 decibels [dB] hearing loss on the audiogram).[16]

All 87 individuals had been treated with methotrexate for over 20 years in remission and were sequentially requested to join the observational trial with audiometry. None of the individuals had cardiac disease, cerebral vascular disease, and all were able to climb a flight of stairs. No patient aged 80–101 was excluded from audiometry and ear examination. Patients were excluded if there was bone or conduction abnormality. Audiometry data collected to assess hearing loss was the average value of the two ear measurements to control for test-retest variance.

All participants signed consent for the audiometry and observational analysis as proposed in a protocol approved by the Western Institutional Review Board (WIRB). Results were provided free of charge to each participant with instructions to discuss the results with their primary physician. A full physical examination, ear examination, medical history, tobacco use history, and a list of concomitant medications was completed for each participant, none of whom were taking any corticosteroid medication.

RESULTS

Of the 87 sequentially enrolled patients, 15 were male and 72 were female. The ages ranged from 80 to 101, with men aged 80–96 and women aged 80–101. The average age among the men was 86.0 years (median: 86.0 years) and the average age among the women was 87.0 years (median: 85.5 years). Quintiles for audiometry exams were defined as normal (1st quintile [Q1]; 0–20 dB), mild impairment (2nd quintile [Q2]; 20–40 dB), moderate impairment (3rd quintile [Q3]; 40–60 dB), moderately severe impairment (4th quintile [Q4]; 60–80 dB), and severe impairment (5th quintile [Q5]; 80–100 dB). Generally, a hearing aid was indicated for Q3, Q4, or Q5. Three male patients (20%) had moderate or moderately severe impairment and one used a hearing aid. Thirty-six (50%) of the elderly female patients had moderate to moderately severe impairment and two used a hearing aid. None of the participants had 'severe' hearing impairment (Q5) upon audiometry examination (Figure 1).

In Q1–Q5, there were 13%, 67%, 13%, 7%, and 0% male patients, respectively, and 16%, 34%, 34%, 16%, and 0% female patients, respectively. There was no statistical difference between males and females according to quintile. In the patient group, 44% qualified for hearing aids (n=39) although only three utilised any hearing enhancement. In analysis of the audiograms, there were no cases of otosclerosis (no Carhart notch), Ménière's disease, or evidence of trauma to the ear. No patient was enrolled if bone or conduction testing was abnormal. Duplicate measurement at the time of the audiogram showed hearing test results were reproducible with little variance.

There was an association between hearing loss and age in the group but this was substantially weaker than expected compared to large normative population studies (Figure 2 and 3).[11,12,17-22] Expected hearing loss is 25% in individuals aged between 55 and 64 years, 43% in individuals aged between 65 and 84, and over 70% in individuals aged between 85 and 100 years old, as recorded by the Beaver Dam Offspring Study of ageing in 3,285 individuals.[17]

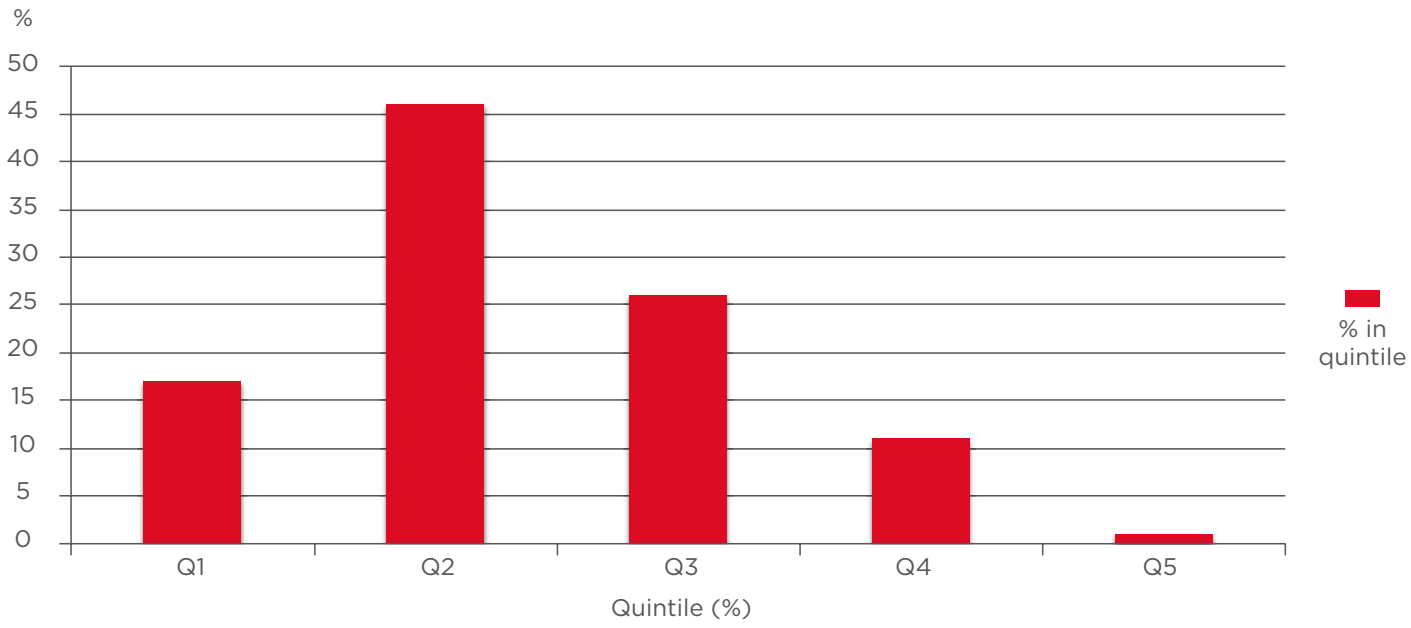

Figure 1: First to fifth quintiles (total: 100%).

Percentage of subjects in each quintile of hearing loss.

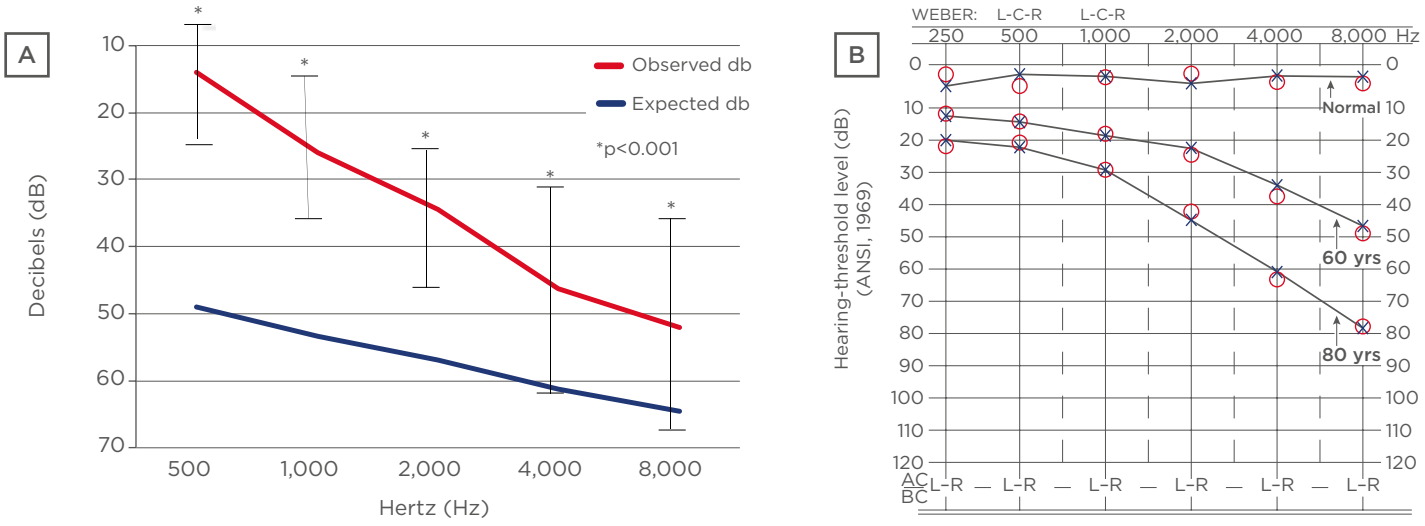

Figure 2: Pure tone audiometry.

(A) Observed cohort versus norms in the general population between 80–101 years old; **(B)** pure tone audiometry expected values in general population by age.
L: left; R: right; yrs: years.

Adapted from Blevins.[20]

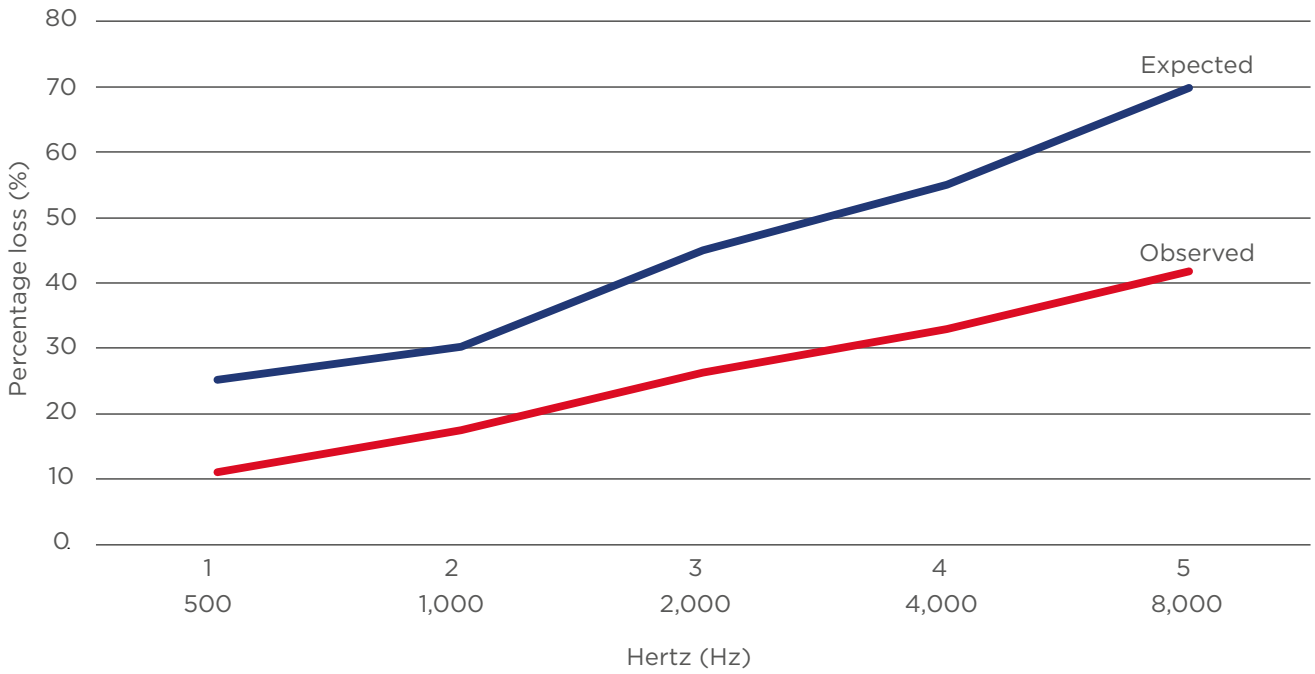

Figure 3: Hearing loss above age 80.

Expected hearing loss with presbycusis and observed measurement of hearing loss in study cohort.

Surprisingly, more than half of the patients in this present study tested as normal or with only mildly-impaired hearing despite advanced age (Q1 or Q2). Each measured audiogram frequency was statistically significantly different compared with preservation of hearing for the normal frequency in the patients aged 80–101 years old ($p<0.001$). Results were not affected when adjusted for multiple variables including sex, tobacco use, statin use, language of origin, education, economic level, or vocation. The patients remained in clinical remission with an average DAS28-ESR 2.0±0.4.

DISCUSSION

The U.S. Preventive Services Task Force (USPSTF) recommends that adults have an audiometry evaluation when they reach 50 years of age and every 3 years thereafter.[23] Audiometry is important to every individual patient since corrections may be made, and presbycusis has a great impact on quality of life, self-esteem, depression, and isolation.[24] The authors' hypothesis was that recognising hearing loss also marks increased risk for atherosclerosis, which may increase patient adherence to lifestyle changes, statins, and blood pressure control.

Normal hearing can range from 20 to 20,000 Hz, but the range of frequencies for understanding speech is 500 to 4,000 Hz. The standard objective test for hearing loss is the pure-tone audiogram, in which a patient is placed in a soundproof booth and tested on ability to hear tones at a series of discrete frequencies. Hearing loss begins with loss at high frequencies which carry the consonant sounds and thus the majority of speech information.

This study tested the 500–4,000 Hz range because it is clinically important and easy to obtain. The audiogram was repeated to obtain a mean of the measurements at each frequency to decrease test-retest error. Routine audiometry should be included in any good clinical practice for persons over 50 years of age, and the hypothesis raised by the observation of this study cohort may reflect early symptoms of atherosclerotic disease. If an audiometry test exists in every clinical chart for persons over 50 years of age, there may be data readily available to assess atherosclerosis risk for each patient. Although

not used in this study, the AudioScope (Welch Allyn Inc., Skaneateles Falls, New York, USA) is a handheld screening instrument consisting of an otoscope with a built-in audiometer. It assesses the ability of patients to hear tones of 20, 25, and 40 dB at frequencies of 500, 1,000, 2,000, and 4,000 Hz and requires approximately 90 seconds to administer.[23]

This observational study attempted to evaluate if there was a correlation between protection against atherosclerosis and preservation of hearing. This was an observational study in the elderly (over 80 years of age), and evaluating audiometry as an atherosclerosis tool will require future studies comparing repeat audiometry measurements to current usage of CT scans, angiography, ultrasound, stress tests, and other radiographic imaging, as well as clinical outcomes such as myocardial infarction and stroke. Current ongoing clinical trials are in progress evaluating PET scan cardiology and concurrent audiometry in patients with high risk of atherosclerosis disease.[25] The hope is that future trials treating atherosclerosis could collect information with audiometry being more cost-effective than repeat imaging, stress tests, or PET scans.

Hearing loss is well documented to progress linearly with age (Figure 2).[20] Hearing amplification is generally indicated for hearing thresholds >40 dB on audiogram (Q3–Q5). Many very elderly patients, generally, would have a hearing aid recommended because most would fall into Q3–Q5; in this study, it was found that 44% (n=39) would benefit from this (Q3 or Q4). Since most with thresholds >40 dB were in Q3, it is possible that people were managing without a hearing aid. It was an unexpected benefit of methotrexate in the patients that hearing was preserved, and most tested one to two decades younger than their age for expected hearing loss. A 100-year-old patient showed the expected results of an 80-year-old patient, and an 80-year-old patient showed the expected results of a 60-year-old patient on audiometry. The auditory technicians also noted preservation of hearing too when evaluating one of the patients on long-term methotrexate. This prompted the early motivation to collect the data in this observation project.

The under-utilisation of hearing aids in the general population was described by Wattamwar K et al.[11] in 2017 in a study of 647 patients aged 80–106 years, where over 80% qualified for hearing aids, but only 59% used any hearing devices.[11] Hearing aids are important when indicated: improved hearing ameliorates isolation, depression, irritating tinnitus, and emotional impact commonly associated with presbycusis.[26]

Hearing loss obviously has an adverse effect on quality of life daily but hearing loss may also reflect atherosclerotic disease resulting in death and cognitive decline. A prospective study by Gates et al.[27] enrolled 274 patients in a surveillance programme of the general population and those at baseline with hearing loss had an increased risk for Alzheimer's disease or cerebral vascular disease over the 4-year follow-up.[27] In another prospective study with 639 normal volunteers over 11 years, those with baseline hearing loss showed a significant increased incidence of cognitive decline,[28,29] presumably due to increased small vessel cerebral disease.[30,31] Hearing loss was a marker for atherosclerosis, both in coronary disease and cognitive function.[32]

The predominant cause for presbycusis is atherosclerosis, but other factors influence hearing over time such as oestrogen levels, traumatic harm to hair cells, cochlear processes, tobacco use, and statin use.[17] Age, after accounting for other variables, accounts for approximately 10% of hearing decline.[12] All 87 patients in this present study had been taking methotrexate for over 20 years and their rheumatoid joints were objectively in remission for many years. Long-term therapy in rheumatoid arthritis with methotrexate has correlated with significant cardiovascular benefit and decreased mortality. Based on published norms, the degree of hearing acuity preserved in this group of elderly patients was unexpected. Hundreds of studies published in the literature have shown methotrexate confers atherosclerotic benefits in rheumatoid arthritis. There are no prior published studies of audiometry in rheumatoid arthritis; rheumatoid arthritis does not cause presbycusis, but the atherosclerosis risk in rheumatoid arthritis may account for the presbycusis. If inflammation is controlled, this results in less atherosclerosis disease and less presbycusis.

Measurement of cognitive decline was minimal in patients from this current study with long-term use of methotrexate, elsewhere reported.[33] It has been noted that hearing loss is linked to increased

dementia and the authors speculated that the study group may have done well on cognitive testing partly because of both this preservation of hearing and decreased cerebral atherosclerosis. The preserved hearing acuity in the group contributed to the high cognitive scores. As atherosclerosis is a cause of presbycusis as well as small vessel vascular dementia, it is possible that interventions for preventing atherosclerosis may be followed using audiometry and cognitive testing beside the traditional outcome measures of myocardial infarction, stroke, and death. Certainly a major limitation of this observational study was that it was not a randomised prospective trial, and the cohort group could only be matched for age and sex, since the normal population cohort used for predicted hearing acuity did not have rheumatoid arthritis. Despite this disparity in the cohort groups, it was clear that the patients had far better hearing, presumably due to treatment of chronic inflammation leading to less atherosclerosis, so that future evaluation of atherosclerosis treatments may include audiometry as an inexpensive assessment.

Results of this population of patients with rheumatoid arthritis treated with methotrexate may not be extrapolated to the general population and this represents a limitation of the hypothesis. There is no comparison group of patients with rheumatoid arthritis after 20 years of disease without methotrexate, so the 'expected' hearing loss with age was drawn from the USA general population in epidemiologic studies for persons over the age of 80. Furthermore, in studies evaluating the concept of inflammation leading to atherosclerosis, methotrexate was not found to suppress cardiovascular events in the general elderly population[34] so there is no comparison elderly group with methotrexate. This study compared the measured audiometry results in the observational group of patients on methotrexate and compared hearing loss to the general population of the same age. In the future, audiometry might prove to be appropriate to assess atherosclerosis in the general population with other therapies such as statins, PCSK9 inhibitors, sodium glucose transport protein inhibitors, or other agents known to suppress inflammation.[35] All of these therapies are approved to reduce atherosclerotic disease in the general population.

CONCLUSION

The authors hypothesised that audiometry as a continuous variable might identify individuals with increasing cardiovascular risk and may prove to be a valuable tool to assess therapy directed toward atherosclerosis. This was a proof-of-concept study in a population at high risk for atherosclerosis, and treated with methotrexate which has been shown to decrease atherosclerosis disease in rheumatoid arthritis.[7] All patients had rheumatoid arthritis treated with long-term methotrexate to reduce atherosclerotic risk, as well as to control the inflammatory disease of arthritis and this study found preserved hearing. Other factors beyond atherosclerosis that co-vary with age contribute to presbycusis, but the authors speculate because of the high contribution of atherosclerosis to hearing loss, that repeat measurement of hearing may offer a useful, practical, and readily available surrogate measure for atherosclerosis progression.

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The Role of Vitamin D in Disease Activity in Axial Spondyloarthritis

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Abstract

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease which predominantly involves the axial skeleton and sacroiliac joints. The aetiology remains unknown but is thought to be immune driven. Vitamin D is a focus for research in numerous autoimmune conditions, especially because it is now thought to have an important role in immunoregulation. It has been hypothesised that low levels of vitamin D increase the risk of autoimmune disease. Considering that vitamin D is implicated in immune regulation and autoimmunity, a question that arises is whether vitamin D deficiency can lead to increased disease activity in axSpA. Through this narrative review of the literature the authors explore potential links between vitamin D and axSpA. This review highlights that larger and more methodologically robust prospective longitudinal studies are required to answer this key question. There was considerable heterogeneity between studies, including in the definition of vitamin D deficiency, latitude where the study took place, and seasonal variation. Another clinically relevant aspect to address is whether correcting vitamin D deficiency leads to improved makers of disease activity in patients with ankylosing spondylitis. This may justify mandatory food fortification and specific supplementation programmes in countries at risk. For example, in Finland there is a low prevalence of vitamin D deficiency in the general population because of food fortification.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease which predominantly involves the axial skeleton and sacroiliac joints; although, peripheral arthritis, enthesitis, and extra-articular features may also be present.[1] The aetiology remains unknown but is thought to be immune driven.[2] AxSpA can be classified into two subgroups: radiographic axSpA, commonly known as ankylosing spondylitis (AS) with defined structural changes in the sacroiliac joints as detected on plain radiography, and nonradiographic axSpA (nr-axSpA). AxSpA is diagnosed by the Assessment of SpondyloArthritis international Society (ASAS) classification criteria.

Table 1: Vitamin D and disease activity in axial spondyloarthritis studies.

Author, year, country Study design Season	Subjects	Controls	Medications: Vitamin D supplement, NSAID, DMARD, biologics	Vitamin D metabolite Deficiency definition	Results
Zhao et al.,[10] 2017, UK Cross-sectional November 2011–November 2015	axSpA 235 patients (AS and axSpA)	None	Vitamin D supplement: included (60 patients) NSAID: 163 DMARD: none Biologics: 74 anti-TNF	25(OH)D <30.0 nmol/L	BASDAI score, ESR, and CRP were higher in vitamin D deficiency.
Yazmalar et al.,[11] 2013, Turkey Cohort July–September and December–February	72 AS (Mod NY criteria); 28 completed the study	71 RA, 74 OA, 70 healthy	Vitamin D supplement: included NSAID: included DMARD: included Biologics: included	25(OH)D Not defined	No difference between groups for vitamin D levels between seasons. BASDAI scores differed between seasons ($p<0.05$). AS had higher CRP levels but not ESR levels. No association between BASDAI score and vitamin D.
Kolahi et al.,[12] 2019, Iran Cross-sectional March–September 2018	86 SpA (AS 65, undifferentiated 14) (International criteria)	117 healthy, age and sex-matched	Vitamin D supplement: excluded NSAID: not mentioned DMARD: not mentioned Biologics: not mentioned	25(OH)D <10.0 nmol/L	Vitamin D was lower in SpA. No correlation with BASDAI score.
Hmamouchi et al.,[13] 2013, Morocco Cross-sectional Summer	70 AS (Mod NY criteria)	140 healthy <65 years	Vitamin D supplement: excluded NSAID: 58 DMARD: none Biologics: 8 anti-TNF	25(OH)D <20.0 nmol/L	Vitamin D was lower in AS group. CRP was higher in AS. Vitamin D negatively correlated with BASDAI score.
Kültür et al.,[8] 2019, Turkey Cross-sectional July 2016–January 2017	62 AS (Mod NY criteria)	32 healthy	Vitamin D supplement: not mentioned NSAID: included DMARD: not mentioned Biologics: included	SVDR Not defined	No difference between SVDR levels between control and AS groups. SVDR levels were higher in AS patients with a BASDAI score >4, compared to controls and inactive AS. No difference between NSAID and anti-TNF therapies. SVDR correlated with ESR and CRP.
Koçyiğit, Akyol,[14] 2018, Turkey Cross-sectional March–May 2018	68 AS (Mod NY criteria)	34 healthy	Vitamin D supplement: excluded NSAID: 36 DMARD: none Biologics: 32 anti-TNF	25(OH)D Not defined	Vitamin D was lower in AS group. No difference in vitamin D between treatment groups. Vitamin D was not associated with BASDAI score, ASDAS-CRP, ESR, or CRP.
Hmamouchi et al.,[15] 2016, France Prospective longitudinal Four seasons	Symptoms suggestive of AxSpA. (IBP criteria, ASAS classification); 486	Healthy from 2006–2007 data	Vitamin D supplement: not mentioned NSAID: included DMARD: not mentioned Biologics: included	25(OH)D <50.0 nmol/L	Vitamin D was lower in DESIR cohort and between winter to spring. Those with vitamin D deficiency at baseline had higher BASDAI scores, but ASDAS was not statistically significant.

Table 1 continued.

Author, year, country Study design Season	Subjects	Controls	Medications: Vitamin D supplement, NSAID, DMARD, biologics	Vitamin D metabolite Deficiency definition	Results
Lange et al.,[16] 2001, Germany Cross-sectional May–August 1998	70 AS (Mod NY criteria)	45 healthy	Vitamin D supplement: not mentioned NSAID: 58 DMARD: 7 MTX, 5 SSZ Biologics: not mentioned	$1,25(OH)_2D$ and 25(OH) D <6.0 ng/mL	AS had higher ESR and CRP and lower $1,25(OH)_2D$ than controls. $1,25(OH)_2D$ negatively correlated with disease activity (ESR, CRP, and BASDAI score).
Žagar et al.,[17] 2019, Croatia Cross-sectional June 2015–April 2016	150 AS (ASAS criteria)	None	Vitamin D supplement: none before study NSAID: not mentioned DMARD: 53 MTX/SSZ/LEF. Biologics: 31 anti-TNF	25(OH)D <50.0 nmol/L	No correlation with BASDAI score, ESR, or CRP and vitamin D. No difference in mean vitamin D concentration through seasons.
Üstün, Turhanoğlu,[18] 2014, Turkey Cross-sectional Winter	75 AS (criteria not mentioned)	35 healthy	Vitamin D supplement: not mentioned NSAID: not mentioned DMARD: not mentioned Biologics: not mentioned	25(OH)D Not defined	Vitamin D was low in both groups. No correlation between vitamin D and BASDAI score.
Erten et al.,[19] 2012, Turkey Cross-sectional Winter: December–March	48 AS (Mod NY criteria), 113 undifferentiated SpA (ESSG criteria)	92 healthy	Vitamin D supplement: not mentioned NSAID: included DMARD: not mentioned Biologics: not mentioned	25(OH)D <10.0 nmol/L	Vitamin D was lower in AS. Vitamin D inversely related to ESR and CRP in AS group only. No correlation between vitamin D and BASDAI score.
Durmus et al.,[19] 2012, Turkey Cross-sectional Unknown	99 AS (Mod NY criteria)	42 healthy	Vitamin D supplement: excluded NSAID: not mentioned DMARD: not mentioned Biologics: not mentioned	25(OH)D <20.0 nmol/L	Vitamin D was lower in AS, but not statistically significant. ESR, CRP, and BASDAI score were higher in vitamin D deficiency subgroup. BASDAI score, ESR, and CRP inversely correlated with vitamin D levels.
Klingberg et al.,[20] 2016, Sweden Cross-sectional February–April 2009	203 AS (Mod NY criteria)	120 healthy	Vitamin D supplement: included (42 patients) NSAID: included DMARD: included Biologics: included	25(OH)D <25.0 nmol/L	No difference in vitamin D levels between groups once those taking supplements were excluded. There was no correlation between vitamin D and ASDAS-CRP, BASDAI score, ESR, or CRP. No difference in vitamin D with those taking NSAID versus anti-TNF versus DMARD.
Mermerci Başkan et al.,[21] 2010, Turkey Cross-sectional Unknown	100 AS (Mod NY criteria)	58 healthy	Vitamin D supplement: not mentioned NSAID: 100 DMARD: 83 SSZ/MTX Biologics: 8 anti-TNF	25(OH)D <20.0 nmol/L	Vitamin D was lower in AS. Negative correlation with vitamin D and ESR/CRP, but not statistically significant. No correlation between vitamin D and BASDAI score.

Table 1 continued.

Author, year, country Study design Season	Subjects	Controls	Medications: Vitamin D supplement, NSAID, DMARD, biologics	Vitamin D metabolite Deficiency definition	Results
Braun-Moscovici et al.,[22] 2011, Israel Cross-sectional Winter and summer	14 AS (Mod NY criteria)	85 RA, 22 PsA	Vitamin D supplement: included NSAID: not mentioned DMARD: included Biologics: included	25(OH)D <12.0 ng/mL = 4.8 nmol/L	No difference with vitamin D and season. No correlation between vitamin D and BASDAI score.
Lange et al.,[23] 2005, Germany Cross-sectional Summer	58 AS (Mod NY criteria)	58 healthy	Vitamin D supplement: not mentioned NSAID: 45 DMARD: 12 MTX/SSZ Biologics: not mentioned	1,25(OH)D <20.0 pg/mL	$1,25(OH)_2D$ was lower in AS group, which negatively correlated with BASDAI score, ESR, and CRP.
Guła et al.,[24] 2018, Poland Cross-sectional Seasonal variation	11 axSpA (ASAS criteria), 29 AS (Mod NY criteria)	12 PsA, 11 perSpA	Vitamin D supplement: included NSAID: included DMARD: included Biologics: included	25(OH)D <30.0 ng/mL = 12.0 nmol/L	No difference in vitamin D levels between axSpA versus perSpA. No association with vitamin D deficiency and BASDAI score, CRP, ESR, or ASDAS. No difference between NSAID or biologic DMARD and vitamin D deficiency. Positive correlation between vitamin D and ESR in axSpA only.
Ozkan et al.,[25] 2017, Turkey Prospective controlled July–September and December–February	32 AS (Mod NY criteria)	25 OA, 25 fibromyalgia, 25 healthy	Vitamin D supplement: excluded NSAID: not mentioned DMARD: not mentioned Biologics: not mentioned	25(OH)D Not defined	No difference in BASDAI score in AS patients between summer and winter, and no association with vitamin D. Vitamin D was lowest in AS winter group but not summer.
Yagiz et al.,[26] 2015, Turkey Retrospective Winter–Spring	100 AS (Mod NY criteria)	92 RA, 62 healthy	Vitamin D supplement: not mentioned NSAID: included DMARD: included Biologics: 29 anti-TNF	25(OH)D <20.0 ng/mL = 8.0 nmol/L	Vitamin D deficiency was common in all groups. Vitamin D levels were not different in AS patients in a subgroup of low versus high disease activity. Treatment groups had no statistically significant correlation with vitamin D level. In AS, vitamin D did not correlate with BASDAI score, ESR, or CRP.
Fernandes et al.,[27] 2018, Global Cross-sectional Four seasons	1,030 SpA–(ASAS criteria)	None	Vitamin D supplement: excluded NSAID: 919 DMARD: 814 Biologics: 499 anti-TNF	25(OH)D <20.0 nmol/L	Vitamin D deficiency was associated with higher BASDAI and ASDAS scores, although observed differences were small. Vitamin D deficiency was associated with radiographic sacroiliitis but there was no difference in MRI sacroiliitis between the two groups.

AS: ankylosing spondylitis; ASAS criteria: Assessment of SpondyloArthritis international Society criteria; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; DESIR: devenir des spondyloarthrites indifférenciées récentes; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; ESSG: European Spondylitis Study Group; IBP: inflammatory back pain; LEF: leflunomide; Mod NY criteria: modified New York criteria for ankylosing spondylitis; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; OA: osteoarthritis; perSpA: peripheral spondyloarthritis; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SpA: spondyloarthritis; SSZ: sulfasalazine; SVDR: serum vitamin D receptor.

Treatments recommended for both conditions include physiotherapy, nonsteroidal anti-inflammatory drugs (NSAID), disease-modifying antirheumatic drugs (DMARD) including methotrexate and sulfasalazine for peripheral arthritis, and biologic therapies including anti-TNF and IL-17A.

Vitamin D has been a focus for research in numerous autoimmune conditions including multiple sclerosis and rheumatoid arthritis.[3] Vitamin D2 (ergocalciferol) is derived from dietary sources, whilst vitamin D3 (colecalciferol) is primarily synthesised in the epidermis through exposure to ultraviolet B (UVB) light. Both vitamins D2 and D3 are converted in the liver and subsequently hydroxylated in the kidneys to form 1,25-dihydroxycholecalciferol ($1,25(OH)_2D$), the active metabolite of vitamin D. The role of vitamin D was previously considered solely for calcium regulation and skeletal homeostasis, but now its role in the immune system is of particular interest. For instance, $1,25(OH)_2D$ has inhibitory effects on dendritic cells, promoting monocyte-to-macrophage differentiation and producing immunosuppressant cytokines.[4] $1,25(OH)_2D$ also promotes increased phagocytic activity of macrophages. Its effect on the acquired immune system includes reducing proinflammatory T-helper 1 and Th17 cell activity, limiting the production of proinflammatory cytokines IL-1, TNF-α, IL-6, and IL-17A.[5] Furthermore, $1,25(OH)_2D$ acts on T regulatory cells and Th2 responses, raising IL-10, an anti-inflammatory cytokine.[5] Vitamin D binds to a nuclear vitamin D receptor (VDR) to either activate or inhibit target genes.[6] It may act to regulate NF-κB activation which is increased in AS.[7] This is important for the expression of adhesion molecules and other proinflammatory genes.[8]

It has been hypothesised that low levels of vitamin D increase the risk of autoimmune disease.[9] Considering vitamin D is implicated in immune regulation and autoimmunity, a question that arises is whether vitamin D deficiency can lead to increased disease activity in axSpA. The objective of this narrative review of the literature is to explore the association between vitamin D and disease activity in axSpA. A search of the current literature was performed on Medline, Embase, and Cochrane using the medical subject heading terms "ankylosing spondylitis," "axial spondyloarthropathy," and "vitamin D." References from review papers were also reviewed for relevance.

HOW COMMON IS VITAMIN D DEFICIENCY IN AXSPA?

Several studies highlighted that vitamin D deficiency is more frequent in patients with AS than in healthy controls (Table 1).[10-27] In a study from Israel, vitamin D levels were shown to be lower in patients with AS than in patients with rheumatoid arthritis and psoriatic arthritis.[22] However, the sample size was small, with only 14 patients with AS included. Frequency of vitamin D deficiency in the study was higher in those of Arabic ethnicity (76.7%) compared to individuals of Jewish ethnicity (23.0%).[22] However, in one of the largest studies examining 203 AS patients from Sweden, no difference in vitamin D levels was found between AS patients and controls. It must be noted that the AS group were older, had higher BMI, had a higher prevalence of tobacco smoking, and were more likely to take vitamin D supplementation than the control group. When patients taking vitamin D supplements were excluded from the results, there was no difference in vitamin D levels between the two groups.[20]

Studies focussing on the association between vitamin D levels and disease activity in AS were predominantly conducted in Europe or in countries bordering the Mediterranean Sea, with the majority taking place in Turkey where vitamin D deficiency is common.[28] A global study (ASAS-COMOSPA) that included patients from 18 countries, with 82.3% located in a latitude greater than 37° North, has shown interesting results.[27] Of the 1,030 patients with spondyloarthritis as defined by the ASAS criteria, 51.2% were found to be deficient in vitamin D.[27] Single-centre studies in North or South America, Australasia, or Asia are lacking.

Vitamin D deficiency is likely to be common in the UK, since one-third of UK adults who had been tested for vitamin D in primary care were found to be deficient.[29] Rates of vitamin D deficiency are also higher in ethnic minority populations in the UK.[29] Global prevalence is difficult to ascertain because of a lack of data, especially from Africa and South America, although an estimated 1 billion people have a vitamin D deficiency.[30,31] Vitamin D deficiency is especially widespread in

the Middle East.[32] Furthermore, Finland, a country with low levels of sunlight, has implemented a national health promotion programme regarding vitamin D supplementation and fortification of milk and dairy products.[33] This has resulted in increased vitamin D intake and higher vitamin D concentrations.[34]

SEASONAL VARIATION ON THE IMPACT OF VITAMIN D

There was significant seasonal variation between studies, with the majority occurring in either the winter or summer. Several studies collected data over a number of seasons. In two studies in Turkey, vitamin D was low in the AS group and control groups over the winter period.[18,26] In a Swedish study, sunlight was not found to be a factor in their results because the study occurred over winter months when UVB levels were too low for synthesis of vitamin D.[20] In comparison, the summer studies found that vitamin D levels remained lower in AS groups than in controls. This included the two studies which measured the active metabolite $1,25(OH)_2D$.[16,23] Widespread deficiency of vitamin D is common throughout the summer, which is interesting because cutaneous synthesis via exposure to UV light is the main source for vitamin D. Five to 10 minutes of sun exposure three times per week is sufficient to guarantee vitamin D supply.[35] People with darker skin absorb more UVB in the melanin of their skin than people with fair skin, and therefore require more sun exposure to produce the same amount of vitamin D.[36,37] Only 10% of vitamin D is provided by the diet.[22]

MEASUREMENT OF VITAMIN D LEVELS

Several studies report on actual 25-hydroxycholecalciferol, or 25(OH)D, levels. However, there were considerable differences in the cut-off values to define vitamin D deficiency. Global consensus to define vitamin D deficiency is lacking. The Endocrine Society definition states a value <50.0 nmol/L, whereas the Institute of Medicine (IOM) committee disagrees with this definition, recommending <30.0 nmol/L to define deficiency,[38] and states that a level >40.0 nmol/L meets the level required for approximately half the population to have good bone health.[39] The range for vitamin D deficiency in the studies evaluated was from 4.8 nmol/L to 50.0 nmol/L, and the median was 20.0 nmol/L. Having a large range makes comparisons between studies difficult, and cut-off values may lead to differences in the interpretation of results. Two studies by Lange et al.[16,23] measured the active metabolite 1,25(OH)2D, which has a short half-life (approximately 4 hours), compared to 25(OH)D which has a half-life of 2–3 weeks.[40] $1,25(OH)_2D$ is also influenced by the VDR, vitamin D-binding protein, and 1-α-hydroxylase, so requires cautious interpretation.[41] Further reasons why the concentration of $1,25(OH)_2D$ cannot be utilised as a marker of vitamin D status are that low concentrations of the final metabolite are detected in the serum, and that a very small amount of 25(OH)D can be converted to $1,25(OH)_2D$ which provide a false idea of sufficiency.[39] It is only when 25(OH)D falls below 10.0 nmol/L that $1,25(OH)_2D$ decreases.[42]

One novel study measured serum VDR (SVDR), where vitamin D binds to activate or inhibit the target genes which play a role in immunological regulation. Polymorphisms of VDR-encoded genes may play a role in the pathogenesis, disease activation, and clinical features of AS.[8] These genes could represent a potential target for modifying disease expression and behaviour.

DISEASE ACTIVITY AND VITAMIN D DEFICIENCY

No clear association has been identified between disease activity and vitamin D deficiency. Studies that found a negative correlation between vitamin D and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) include one study that recruited male patients only.[13] Raised inflammatory markers, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and BASDAI scores have been shown to be higher in AS patients with vitamin D deficiency compared to AS patients with normal vitamin D levels.[19] Serum $1,25(OH)_2D$, the active metabolite, is also negatively correlated with ESR, CRP, and BASDAI scores in patients with AS.[16,23] In the DESIR cohort, a prospective observational study, vitamin D deficiency was associated with higher BASDAI and Ankylosing Spondylitis Disease Activity (ASDAS) scores, although ASDAS scores were not statistically significant.[15] Vitamin D deficiency was also

associated with radiological sacroiliitis at baseline assessment.[15] The inclusion criteria for this study, however, were patients with inflammatory back pain suggestive of spondyloarthritis who were subsequently classified according to the ASAS criteria. Serum VDR levels were positively correlated with BASDAI, CRP, and ESR.[8] In the ASAS-COMOSPA study, patients with vitamin D deficiency had higher BASDAI and ASDAS scores than those with normal vitamin D levels, although the observed differences were small.[27] Radiographic sacroiliitis was also more prevalent in the vitamin D-deficient group, but there was no difference in MRI sacroiliitis between the two groups. Two limitations to this study were that serum vitamin D levels were derived from a variety of laboratory methods, and 239 patients with psoriasis and 53 patients with inflammatory bowel disease were included in the study.[27]

Several studies found no association between vitamin D deficiency and increased disease activity as measured by BASDAI.[11,12,14] There was also no association with vitamin D level and ASDAS-CRP.[20] There was a positive correlation between vitamin D levels and ESR in patients with axSpA, but no association with vitamin D deficiency and BASDAI, CRP, and ASDAS. The authors could not explain this result.[24]

Evidence from Systematic Reviews and Meta-Analyses

A meta-analysis by Cai et al.[3] found that higher levels of disease activity were present in patients with low vitamin D levels. Vitamin D deficiency was also associated with AS susceptibility. However, the heterogeneity of the studies (I^2=90%) makes comparisons between studies difficult. Only eight studies were included in the meta-analysis and most were from Chinese databases, which were not included in the present narrative review. A systematic review by Zhao et al.[41] in 2014 found that vitamin D was lower in patients with AS, but there were insufficient published data to support an immunomodulatory role for vitamin D in AS. No studies included in the systematic review were prospective longitudinal studies.

Another systematic review by Kriegel et al.,[43] which evaluated whether vitamin D affects the risk of developing an autoimmune disease, concluded that cross-sectional data pointed to a potential role of vitamin D in autoimmune disease prevention. Only four case-controlled studies for patients with AS were included, two of which measured the active metabolite $1,25(OH)_2D$ which has its limitations as previously discussed.[16,23] Another study by Mermerci Başkan et al.[21] found no association between vitamin D and BASDAI, and a further study found a negative correlation between CRP and vitamin D in a combined cohort of AS and psoriatic arthritis patients. [44]

VITAMIN D SUPPLEMENTATION

In the studies evaluated, most did not mention in their methods if patients were taking vitamin D supplementation. Five studies[10,11,20,22,24] included information on supplementation and seven studies[12-14,17,19,25,27] excluded vitamin D supplementation. No difference in disease activity, as measured by BASDAI, ASDAS, CRP, and ESR, was found in patients with AS and nr-axSpA once adjusted for vitamin D supplementation.[24] Comparisons between AS and nr-axSpA as subgroups were not performed. Dietary intake of vitamin D included fortified foods and was not taken into consideration in all studies. This was unlike a prospective controlled study of 40 patients with AS who had disease activity measured in the summer and winter.[25] Patients taking calcium and vitamin D supplements were excluded from the study. There were no differences between dietary habits of patients with AS versus controls who had either osteoarthritis or fibromyalgia. However, the results do not include these data, and the methodology does not explain how dietary information was obtained and classified. Mean BASDAI value in the AS group did not show any significant difference between summer and winter, and there was no correlation between vitamin D and BASDAI in both seasons.

THE ROLE OF DISEASE-MODIFYING ANTIRHEUMATIC DRUG THERAPIES ON VITAMIN D

Studies generally show no statistically significant correlations between vitamin D deficiency and anti-TNF therapy or DMARD.[14,20] Patients treated with anti-TNF had lower BASDAI scores but vitamin D levels were similar to those treated with

DMARD.[22] When SVDR levels were measured, a significant difference was found between patients taking NSAID versus anti-TNF biologic therapy.[8] Anti-TNF therapy may suppress SVDR. In addition, SVDR levels of the AS group treated with NSAID were elevated compared to the control group.[8]

KEY LEARNING POINTS

Studies that focussed on vitamin D levels and disease activity in AS demonstrate considerable heterogeneity, including the definition of vitamin D deficiency, latitude where the study took place, and seasonal variation. Disease duration and severity of disease were often not taken into consideration which may implicate the findings to date. Sample size for a number of the studies was small, which is another important limitation. This makes the identification of causative links between vitamin D and disease activity difficult.

Vitamin D levels were often lower in patients with AS compared to controls, although in a large proportion of the studies vitamin D levels were low in both groups. Furthermore, patients with active disease are likely to be less mobile and subsequently are less likely to receive sun exposure. It is hypothesised that autoimmune disease incidence is associated with latitude. This may be explained by genetics, diet, infection, or exposure to UVB. In the studies evaluated, most occurred between the latitude 30–40°, which are associated with good levels of sunlight all year round. Patients from Morocco and Turkey often had low vitamin D levels, which is likely caused by a combination of genetic, dietary, and clothing attire factors. In a Swedish study, sunlight was not a factor in their results because the study occurred over winter when UVB levels were too low for synthesis of vitamin D,[20] which again suggests that genetic and dietary factors play an important role in influencing vitamin D levels. None of the studies provided evidence that the incidence for AS may be higher in countries with widespread vitamin D deficiency compared to those without.

The greatest challenge in robustly determining if vitamin D deficiency is associated with increased disease activity was the lack of prospective longitudinal studies. To date, only two of the studies are prospective longitudinal studies. One included only 32 patients with AS, but found no association between vitamin D levels and BASDAI scores, with no change in BASDAI score between winter and summer.[25] The other prospective longitudinal study included patients presenting with inflammatory back pain suggestive of axSpA. Patients were subdivided into three groups: those who met ASAS criteria with imaging changes, those who met ASAS criteria with clinical parameters, and those who did not fulfil ASAS criteria. The modified New York criteria were not included in this study. The main finding was of a higher prevalence of vitamin D deficiency in spondyloarthritis at the onset of disease, which may correlate with more active and severe disease. This was supported by findings of greater prevalence of baseline radiological sacroiliitis in those with vitamin D deficiency. The level of vitamin D was negatively correlated with BASDAI and ASDAS score.[15] Cross-sectional studies often only measured a 'snapshot' measurement of vitamin D, introducing bias and unexplained variability when level of sunlight exposure, dietary intake, and control for seasonal variation was poor.

A limitation in the disease activity reported in the studies is that patients often have normal serum inflammatory markers despite evidence for bone marrow oedema on MRI. Furthermore, vitamin D deficiency in healthy populations can manifest as arthralgia, and BASDAI scores in patients with vitamin D deficiency may be higher as a result. The same applies to patients with secondary fibromyalgia, which has a high prevalence in AS. Fibromyalgia was not mentioned as an exclusion criterion in any of the studies. A more accurate assessment for disease activity would incorporate spinal imaging with BASDAI measurements.

CONCLUSION

In summary, larger and more methodologically robust prospective longitudinal studies are required to determine whether vitamin D is related to disease activity. Another clinically relevant aspect to address is whether correcting vitamin D deficiency leads to improved makers of disease activity in patients with AS. This may justify mandatory food fortification and specific supplementation programmes in countries at risk.

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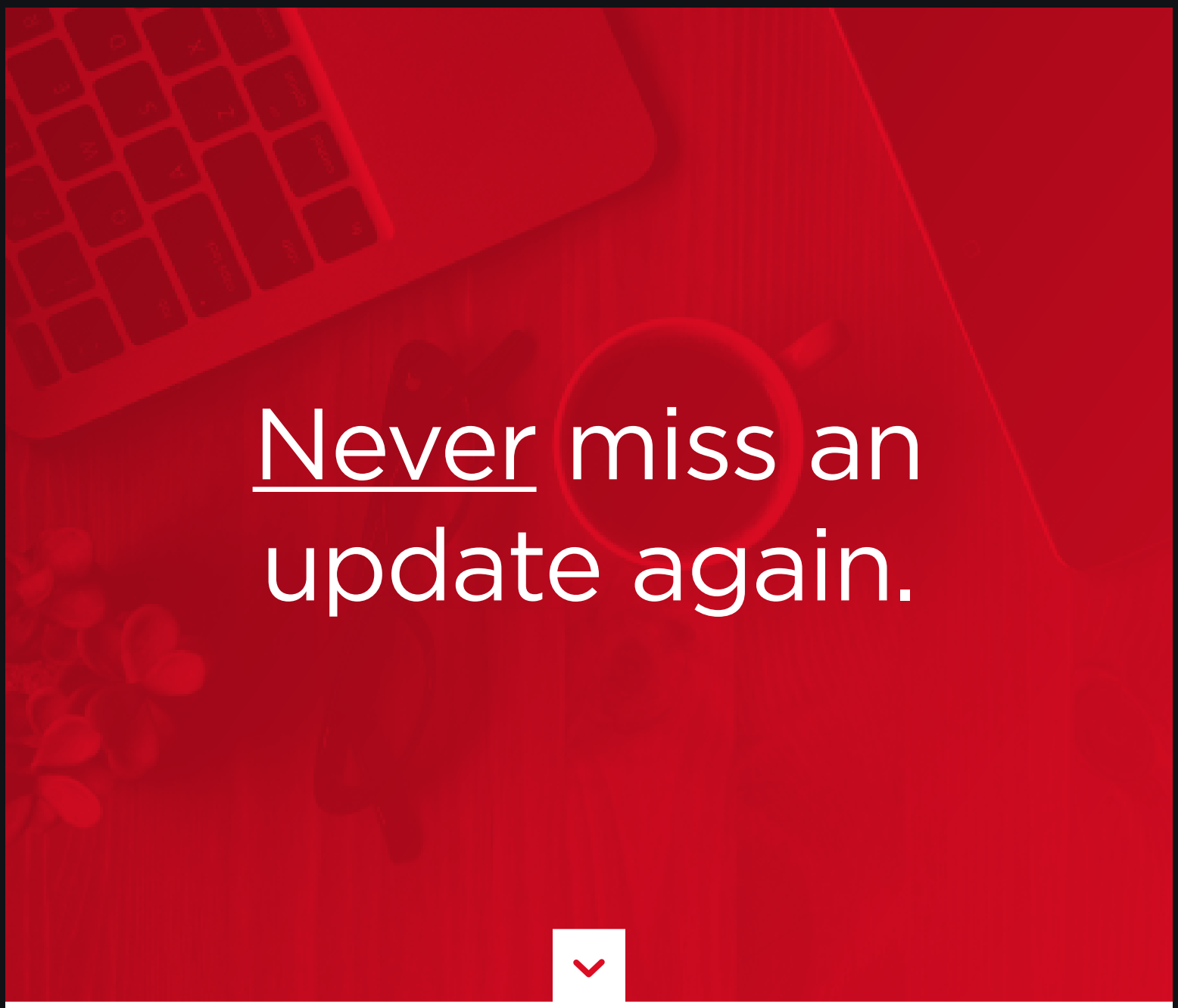

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