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EMJ Rheumatology

Review of EULAR Congress 2022

Editor's Pick

Paediatric Scleroderma: Kids Are Not Just Little Adults

Interviews

Xenofon Baraliakos provides insights into EULAR 2022, while Jeffrey Sparks and Lorinda Chung discuss their careers and influential research

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Contents

Features

Articles

Editorial Board

Aims and Scope

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Front cover and contents photograph: Copenhagen, Denmark, home of the **EULAR 2022**. © XXX / stock.adobe.com

Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Dear Readers,

It is a great pleasure to welcome you to the 2022 issue of *EMJ Rheumatology*. This year's Congress of the European Alliance of Associations for Rheumatology (EULAR) took place in Copenhagen, Denmark, and we have the pleasure of bringing you the key highlights from this event.

Some interesting themes from this year's congress included disparities in access to rheumatology care, harmonisation of rheumatology training across the European Union (EU), patient empowerment, and pregnancy outcomes in females with rheumatic disease, among others. In our congress review, you will have the opportunity to read about difficult-to-treat arthritis, as presented at the congress. We are delighted to also feature an interview by Xenofon Baraliakos, who is a member of the EULAR Congress Committee.

An engaging opinion piece published in the journal focuses on multisystem inflammatory syndrome in children and Kawasaki disease. We are also pleased to showcase a highly interesting review of ocular manifestations of Loeys–Dietz syndrome and a clinical image case of a self-resolving flare of psoriasis after COVID-19 vaccination, a first ever in our journal.

I hope that you enjoy the new brighter and bolder look of our brand and journals. The learning points added to the start of longer articles aim to elevate the experience for our readers. I would like to close by thanking our Editorial Board, authors, and peer reviewers, who have helped bring together this fantastic selection of content, and I hope that you enjoy reading through the issue.

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Foreword

Dear Colleagues,

It is a great pleasure to present the 2022 issue of *EMJ Rheumatology*. As with previous issues, several disease areas have been discussed in peer-reviewed papers.

The Editor's Pick in this issue is a paper by Li and McCormick, which reviews the clinical presentation patterns and morbidities associated with paediatric-onset juvenile localised scleroderma and juvenile systemic sclerosis. This paper highlights the key differences in disease patterns, which may influence targeted therapy approaches. A major challenge is early diagnosis and intervention to prevent disease progression, as the early stages of scleroderma may be difficult to identify.

The role of genomics in medicine is highlighted in the paper by Loomba et al. that reviews the ocular manifestations of Loeys–Dietz syndrome, which will be of interest to both rheumatologists and ophthalmologists. Sun et al. review the role of interferons (IFN) in Sjögren's syndrome (SS). Three types of IFNs play a role in the pathogenesis of SS. The role of Type 1 IFN in the pathogenesis of SS is reviewed, opening new avenues for targeted therapies, some of which are in clinical trials.

There is a debate on whether the multisystem inflammatory syndrome described in paediatric COVID-19 infection and Kawasaki disease are the same inflammatory manifestations. Mangat et al. review the overlapping clinical presentations and highlight some differentiating features; however, the management is almost the same.

For those who were unable to addend the European Alliance of Associations for Rheumatology (EULAR) 2022 Congress, I recommend our independent congress review on the late-breaking research, abstract highlights, and an in-house feature discussing difficult-to-treat rheumatoid arthritis.

As Editor-in-Chief, I thank all the authors, reviewers, and Editorial Board members who contributed to the success of this issue of *EMJ Rheumatology*. I hope this issue will extend your boundaries of medical science and be a valuable resource in your everyday clinical practice.

With kind regards,

Ian C Chikanza

Consultant in Adult & Paediatric Rheumatology, Department of Rheumatology, Barts & the Royal London Hospital, London, UK; Professor of Medicine, Catholic University and Prof in Rheumatology & Immunology, University of Zimbabwe, Harare, Zimbabwe

EULAR 2022

Review of the European Alliance of Associations for Rheumatology (EULAR) 2022 Congress

Location: Copenhagen, Denmark

Date: 1st–4th June 2022

Citation: Citation: EMJ Rheumatol. 2022;9[1]:8-16. DOI/10.33590/emjrheumatol/22E0714. https://doi.org/10.33590/emjrheumatol/22E0714.

A NEW and innovative hybrid format was adopted for the European Alliance of Associations for Rheumatology (EULAR) 2022 Congress, allowing delegates to meet on-site in Copenhagen, Denmark, and online. This year, EULAR celebrates its 75th anniversary, and the Opening Plenary Session focused not only on the association's biggest achievements over the years, but also what to expect from the future.

EULAR Past President Iain McInnes reflected on the association's "extraordinary contribution to this past that we are celebrating." McInnes emphasised that EULAR is primarily focused on people with rheumatic and musculoskeletal diseases. "In this regard, we are very proud of the recommendations and treatment strategies that have been pioneered to optimise care," he said. Through the work of standing committees and task forces, EULAR has "optimised the integration of new technology," added McInnes. This is best exemplified most recently in the advent of imaging modalities, which have further transformed care. "Finally, through our world-class congress and our increasingly persuasive advocacy programme, EULAR has spoken, and speaks, with passion and purpose to advance the cause of people with rheumatic and musculoskeletal diseases in the educational, political, and wider domain," revealed McInnes. Although it cannot be said with certainty what will happen over the next 75 years, McInnes is confident that EULAR will continue to "strive on behalf of our patients, without reservation or limitation."

EULAR President Annamaria Iagnocco also discussed the future of the organisation in her welcome speech, and considered how EULAR can continue to advance rheumatological care across Europe. Rheumatic and musculoskeletal diseases are disabling and burdensome, and have a high prevalence, affecting more than 120 million Europeans. However, disparities remain in patient access to rheumatology departments. "To help solve this problem, we must position rheumatology as an important, interesting, and essential field of medicine, that is seen at the same level as other major specialties," stated Iagnocco.

Going forward, it is imperative to increase access to care, improve rheumatology visibility to policymakers and the public, and make the discipline attractive to medical students when they chose their specialisation. The

Danish rheumatology workforce was used to illustrate how this can be achieved. In Denmark, there are 29 rheumatologists per 500,000 inhabitants, and this can be attributed to the excellent medical education. Moreover, the Danish model is notable for focusing on the principle of togetherness. Diverse healthcare professionals collaborate with rheumatologists in a multidisciplinary team to support patients and offer guidance on non-pharmacological treatment options. Importantly, patients are proactively involved in decision making at every stage of the process, from symptom onset to goal setting. A prime example of this collaboration is the Dansk Gigthospital in Sønderborg, which is owned directly by the Danish Rheumatism Association. Within this one hospital, rheumatologists work closely with professors for rheumatologic rehabilitation, nurses, occupational therapists, physiotherapists, psychologists, and the patient organisation itself. Ultimately, patient-centred, multidisciplinary care is a valuable way of building trust, enhancing treatment adherence, and preventing comorbidities. Patients are also provided with rapid access to rheumatologists. For example, new patients should wait no longer than 4 weeks for access to a specialist appointment, and this is guaranteed by Danish law.

As with previous EULAR conferences, the 2022 congress was crucial for the generation and exchange of scientific knowledge. Symposia spanned across the discipline, providing updates on gastrointestinal manifestations in systemic sclerosis and myositis, the role of ultrasound in calcium pyrophosphate deposition, the challenge of pregnancy in rheumatic disease, and clinical challenges in systemic lupus erythematosus. Of particular interest was the session on difficult-to-treat rheumatoid arthritis, which forms the basis of our compelling in-house feature.

An overview of standout EULAR press releases can be found within this issue of *EMJ Rheumatology*, including insights into treatment effectiveness in people with axial spondyloarthritis, the importance of treatment goals in psoriatic arthritis, and the association between air pollution and the development of inflammatory arthritis.

Our interview with EULAR Treasurer Xenofon Baraliakos is also not to be missed. Baraliakos talked about the effects of secukinumab in patients with psoriatic arthritis and axial manifestations, his responsibilities as a EULAR committee member, and patient-tailored treatment in the context of axial arthritis and psoriatic arthritis.

We look forward to being part of the international rheumatology community again at next year's congress. Until then, read on for our key scientific insights from EULAR 2022 Congress.

Inflammatory Arthritis Development Driven by Air Pollution

NEW EVIDENCE on the links between rheumatic disease and pollutants was shared at the EULAR 2022 Congress in Copenhagen, Denmark. Air pollution has been found to be a key environmental exposure exacerbating the development of inflammatory arthritis and affects the immune system on a molecular level.

Data presented show that long-term exposure to air pollution is associated with incremental risks in the development of rheumatic disease. Two abstracts, which were presented by Giovanni Adami, Rheumatology Unit, University of Verona, Italy, focused on environmental exposures, and their role in the occurrence of rheumatic disease.

Data taken from over 80,000 individuals in a retrospective observational study carried out in Italy focused on particulate matter (PM), every non-gas found in the air. This contains chemicals and materials, some of which are toxic. Researchers found there to be a positive association between levels of PM measured at local air quality stations, and the risk of developing autoimmune diseases. Each 10 µg/m^3 increase in the concentration of PM correlated with a 7% risk of having autoimmune disease.

Exposure to PM_{10} was linked with increased risks of rheumatoid arthritis, and $PM_{2.5}$ was consistent with an increased risk of both rheumatoid arthritis and inflammatory bowel disease. Chronic exposure to PM levels above the safe threshold was found to be associated with a 10% greater risk of developing immune-mediated disease.

"Data presented show that long-term exposure to air pollution is associated with incremental risks in the development of rheumatic disease."

Exposure to $PM_{2.5}$ in a group of almost 60,000 females at high risk of fracture was found to be negatively associated with osteopenia at the top of the thigh bone, and in the lumbar spine. Persistent exposure above 25 µg/m^3 for $PM_{2.5}$ and 30 µg/m^3 for PM_{10} was associated with a 16% and 15% higher risk of having osteoporotic bone mass scores, respectively. Adami and his team concluded that a higher risk of osteoporosis was linked with long-term exposure to air pollution in the environment. ●

Treatment Effectiveness for Axial Spondyloarthritis

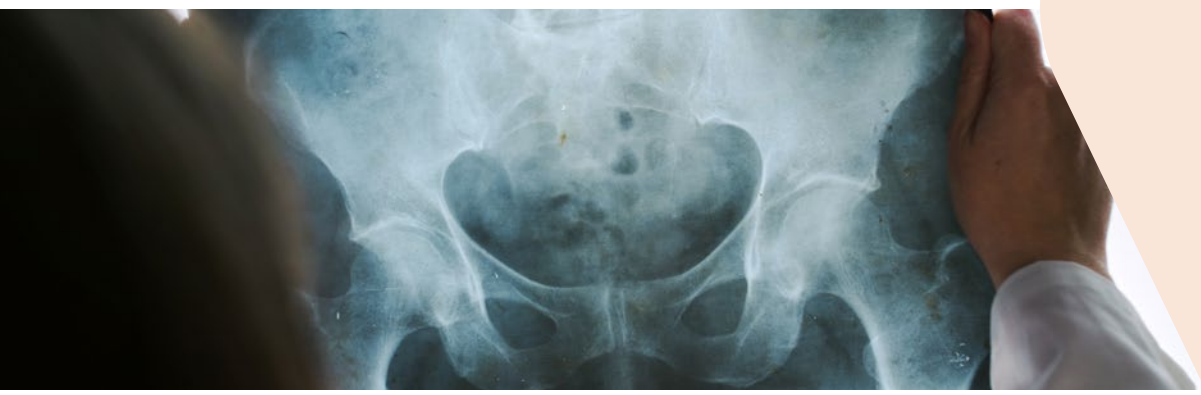
RESEARCHERS have presented new evidence at the EULAR 2022 Congress, held in Copenhagen, Denmark, revealing sex differences in disease presentation, physiology, and response to treatment in patients with axial spondyloarthritis (axSpA). This is a chronic inflammatory rheumatic disease that affects the spine and sacroiliac joints, and can cause persistent pain and disability.

Treatments for axSpA are wide-ranging, but a tailored approach is needed, as their effectiveness varies greatly between patients. The use of TNF inhibitors, for instance, has been found to have more efficacy in males than females with axSpA in previous data. Recognising differences in treatment efficacy between sexes is highly relevant in order to tailor patient care and also to improve patient education.

Pasoon Hellamand, Rheumatology, Amsterdam UMC, the Netherlands, and colleagues aimed to validate the results of prior studies by using data collected from a large multinational cohort in a clinical practice setting. In the study, 6,451 patients with axSpA were assessed regarding their treatment response. Analysis demonstrated that females showed a 15% lower clinically important improvement when compared with males with the same condition. Retention rates of TNF inhibitors were also found to be significantly lower in the female cohort. The research team also focused upon the impact of non-steroidal anti-inflammatory drugs (NSAID) used in the treatment of patients diagnosed with radiographic disease.

"Recognising differences in treatment efficacy between sexes is highly relevant in order to tailor patient care, and also to improve patient education."

Another group, led by Murat Torgutalp, Charité – Universitätsmedizin Berlin, Germany, focused on whether treatment with NSAIDs is linked to delaying the progress of radiographic spinal progression. The data thus far has shown conflicting reports. The group of researchers studied 243 patients with early axSpA from the German Spondyloarthritis Inception Cohort (GESPIC) in order to establish the link between NSAID intake and radiographic spinal progression over a 2-year period. The results demonstrated that higher intake of NSAID is associated with lower radiographic spinal progression, especially in patients diagnosed with radiographic axSpA. ●



Treatment Goals in Psoriatic Arthritis

RECENT DATA have shown that the early achievement of minimal disease activity (MDA) in psoriatic arthritis (PsA), a type of inflammatory arthritis which is linked to the chronic skin condition psoriasis, is connected to long-term improvements in the patient's quality of life (QoL). Whilst this emphasises the significance of setting and achieving goals quickly following diagnosis, data released from the UPLIFT study suggest that healthcare providers and patients are often unaligned on the topic of treatment goals.

The results, which were presented at this year's EULAR Congress in Copenhagen, Denmark, highlighted the necessity of improving communication around the topic of treatment goals, which would consequently ameliorate the QoL for patients with PsA. Patients with PsA experience swelling and pain in both their joints and at the places where tendons and ligaments attach to bones. MDA is a target used in PsA treatment, which makes use of the patient perspective alongside clinical manifestations of disease.

Achieving MDA in the initial year following diagnosis is associated with a better quality of life; however, data regarding reaching MDA after this period have been lacking thus far. Information presented by Selinde Snoeck Henkemans, Rheumatology, Erasmus MC, Rotterdam, the Netherlands, demonstrated that patients with PSA with a sustained level of MDA have a QoL comparable to the general disease-free population after 1, 2, and 3 years of follow-up, respectively. Those who did not reach MDA in the first year after diagnosis, however, generally had a lower QoL in comparison and this persisted over time. Snoeck Henkemans concluded that the failure to achieve MDA in PsA in the first year following diagnosis tends to be associated with worse QoL outcomes, which do not improve despite intensified treatment.

> **"Data released from the UPLIFT study suggest that healthcare providers and patients are often unaligned on the topic of treatment goals."**

Another study released at EULAR 2022 supports these findings. Pascal Richette and his team focused on findings from UPLIFT, a multinational survey for adult patients with PsA and/or psoriasis, and included information from rheumatologists and dermatologists. Richette's study found that rheumatologists considered disease remission or low disease activity as pivotal goals in the treatment of PsA, but patients were most interested in alleviating joint pain. Thus, the majority of patients did not believe that they were aligned with their healthcare provider regarding current treatment goals. ●

Alternatives to Opioid Pain Management in Rheumatic and Musculoskeletal Diseases

RHEUMATIC and musculoskeletal diseases (RMD) are one of the most common indications for prescribed opioids. Pain is an important consideration for patients with RMDs, which can restrict function and impact quality of life. However, there is little evidence for the benefit opioids provide these patients, and opioid prescription has led to a North American epidemic of addiction, with increasing trends observed in several European countries as well. Several abstracts presented at the EULAR 2022 Congress aimed to address the lack of knowledge about pain management in RMD and develop novel pain relief strategies to reduce this chronic health burden.

"Several abstracts presented at the EULAR 2022 Congress aimed to address the lack of knowledge about pain-management in RMD, and develop novel pain-relief strategies to reduce this chronic health burden."

The current standard pain treatment for patients with RMDs is the injection of steroids; however, this can increase risk of infection, cartilage degeneration, and induce other well-known systemic side effects. An abstract presented by Hildrun Haibel, Department of Gastroenterology, Infectious Diseases and Rheumatology, Charité – Universitätsmedizin Berlin, Germany, investigated a new approach to pain management focusing on the activation of peripheral opioid receptors using small doses of morphine in adults with chronic knee arthritis. The results demonstrated that a single-dose 3 mg morphine injection did not lead to significant pain improvements compared with a placebo, and showed inferior pain improvements relative to steroid treatment on Day 7.

A second abstract presented by Joyce (Yun-Ting) Huang, Department of Epidemiology and Public Health, University College London, UK, analysed UK opioid prescribing trends to first-time users with an RMD diagnosis. The data showed an increase in new opioid users among patients with rheumatoid arthritis, psoriatic arthritis, and fibromyalgia since 2006. However, overall, the results demonstrated a small decrease in new opioid users among most RMDs. The authors hypothesised that this decrease, which occurred after 2008, may have been related to increasing awareness about the opioid epidemic. The high proportion of long-term opioid users in patients with rheumatoid arthritis and fibromyalgia highlights the importance of exploring the safety of long-term opioid use and effective pain interventions.

A third abstract presented at EULAR looked at alternative strategies for reducing the burden of lower back pain. Jacek Kopec, School of Population and Public Health, University of British Columbia, Vancouver, Canada, and his team investigated weight loss, ergonomic interventions, and an exercise programme. This population-based microsimulation study found that a one-unit reduction in BMI per year among overweight and obese individuals produced a reduction in disability equivalent to an effective ergonomic intervention in 35% of at-risk workers.

Pregnancy Outcomes in Females with Rheumatic and Systemic Autoimmune Diseases

NEW data presented at the EULAR 2022 Congress showed an increase in adverse outcomes in females who are pregnant with various rheumatic and systemic autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, and systemic lupus erythematosus (SLE). The study reported that fetal and serious maternal morbidity happen at an increased rate in females with SLE relative to females without SLE. Additionally, the increased risk was noted in females with spondyloarthritis (SpA), which was associated with the use of steroids in females with rheumatoid arthritis.

In SpA, the results have not been aligned as some studies report increased pregnancy risks while others have failed to identify any notable distinction between females with and without SpA. Bella Mehta presented findings from a retrospective study on delivery-related hospital admissions of more than 50,000 females with SLE. The study group found that patients with SLE had a greater risk of fetal morbidity, which included a higher risk of intrauterine growth restriction and preterm delivery. Furthermore, patients with SLE also had a higher risk of general medical issues (e.g., blood transfusion, puerperal cerebrovascular disorders, acute renal failure, eclampsia or disseminated intravascular coagulation, and cardiovascular and peripheral vascular disorders) than those without SLE. These new findings will assist in pregnancy management in females with SLE.

"NEW data presented at the EULAR 2022 Congress shows an increase in adverse outcomes in females who are pregnant with various rheumatic and systemic autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, and systemic lupus erythematosus."

Another study presented results from a nationwide register-based study of singleton births between April 2007 and December 2019 in females diagnosed with ankylosing spondylitis or undifferentiated SpA. This study confirmed that females with SpA had a greater risk of adverse outcomes in their pregnancies, including a higher risk of developing gestational diabetes, elective and emergency caesarean delivery, and preterm birth. Additionally, children born to females with SpA were not necessarily smaller but had an increased chance of developing infection in the first year. To conclude the session, another study showed the impact of rheumatoid arthritis and its treatment in 92 females. A positive pregnancy outcome was reported in 56.5% of the participants. Small for gestational age (20.5%) and premature birth (16.9%) were the most common unfavourable outcomes.

Rheumatic and Musculoskeletal Diseases not Risk Group for Severe COVID-19 Infection

ACCORDING to data presented at the EULAR 2022 Congress, patients with inflammatory rheumatic diseases (IRD) should not be considered a risk group for severe COVID-19. The studies supported the overall advice of administering three doses of COVID-19 vaccine, particularly in older patients and patients receiving immunomodulatory treatment.

The researchers collated data from two large ongoing prospective cohort studies and explored the post-vaccination serum samples for evidence of breakthrough infection. It was observed that the occurrence of breakthrough infections was similar between patients taking immunosuppressants and controls. Additionally, hospitalisation occurred in similar proportions in both groups. Generally, hospitalised cases had more comorbidities and were older relative to non-hospitalised cases.

Patients treated with anti-cluster of differentiation 20 therapy, in comparison to any other immunosuppressant, had significantly higher hospitalisation rates. Despite the fact that anti-cluster of differentiation 20 therapy may increase the chances of severe COVID-19 breakthrough infections, the researches believed traditional risk factors continue to make a significant contribution. In conclusion, patients with IRDs should not necessarily be viewed as a risk group for severe COVID-19, and incorporating other risk factors should be standard practice when considering treatment options, vaccination, and adherence to infection prevention measures.

> **"Patients with inflammatory rheumatic diseases (IRD) should not be considered a risk group for severe COVID-19."**

Another study presented at this year's congress used the German COVID-19-IRD registry as of 31st January 2022. A total of 271 breakthrough infection cases were reported. In these cases, 91% of the patients had received two doses of the vaccine and 9% had received three doses, with an average time of 148 days between the last dose and infection. Patients who had been triple vaccinated had a higher rate of comorbidities; however, patients infected displayed a lower rate of hospitalisation, COVID-19-associated complications, requirement of oxygen treatment, or death. Both studies support the overall endorsement of reducing risk of severe COVID-19 by administering three doses, especially in more vulnerable patients. ●

EULAR 2022

Difficult-to-Treat Rheumatoid Arthritis

Author: Theo Wolf, Senior Editorial Assistant

Citation: EMJ Rheumatol. 2022;10[1]:17-20. DOI/10.33590/emjrheuma-tol/22F0714. https://doi.org/10.33590/emjrheumatol/22F0714.

At this year's European Alliance of Associations for Rheumatology (EULAR) Congress, taking place on 1st–4th June, Jacob van Laar, Professor of Rheumatology, University Medical Center Utrecht, the Netherlands, provided insights into strategies to manage patients with difficult-to-treat rheumatoid arthritis.

DIFFICULT-TO-TREAT RHEUMATOID ARTHRITIS: A CASE

Van Laar began by discussing the case of a 60-year-old female with obesity who was diagnosed with rheumatoid arthritis 15 years earlier. The patient had cycled through the common conventional disease-modifying antirheumatic drugs (DMARD), including many of the biologic DMARDs as well. Her medical history also included deep vein thrombosis, debridement of the right knee because of a torn meniscus, total knee replacement on the right side, and ischaemic heart disease. The patient's current symptoms included fatigue; morning stiffness lasting 2 hours; and pain in the hands, feet, wrists, shoulders, and elbows. She was taking prednisolone as monotherapy (7.5 mg), and had started taking celecoxib (200 mg twice daily). However, this combination of treatments was not sufficient to reach low disease activity.

On physical examination, the patient had a BMI of 32, and skin atrophy with haematomas. Rheumatological investigation revealed synovitis in both wrists. Laboratory findings demonstrated an acute-phase response, and confirmed that the patient was double positive for rheumatoid factor and anti-cyclic citrullinated peptides. Van Laar also noted that the patient always had some disease activity, sometimes severe and sometimes moderate, despite all kinds of treatments, and had failed multiple conventional and biological DMARDS.

DEFINING DIFFICULT-TO-TREAT RHEUMATOID ARTHRITIS

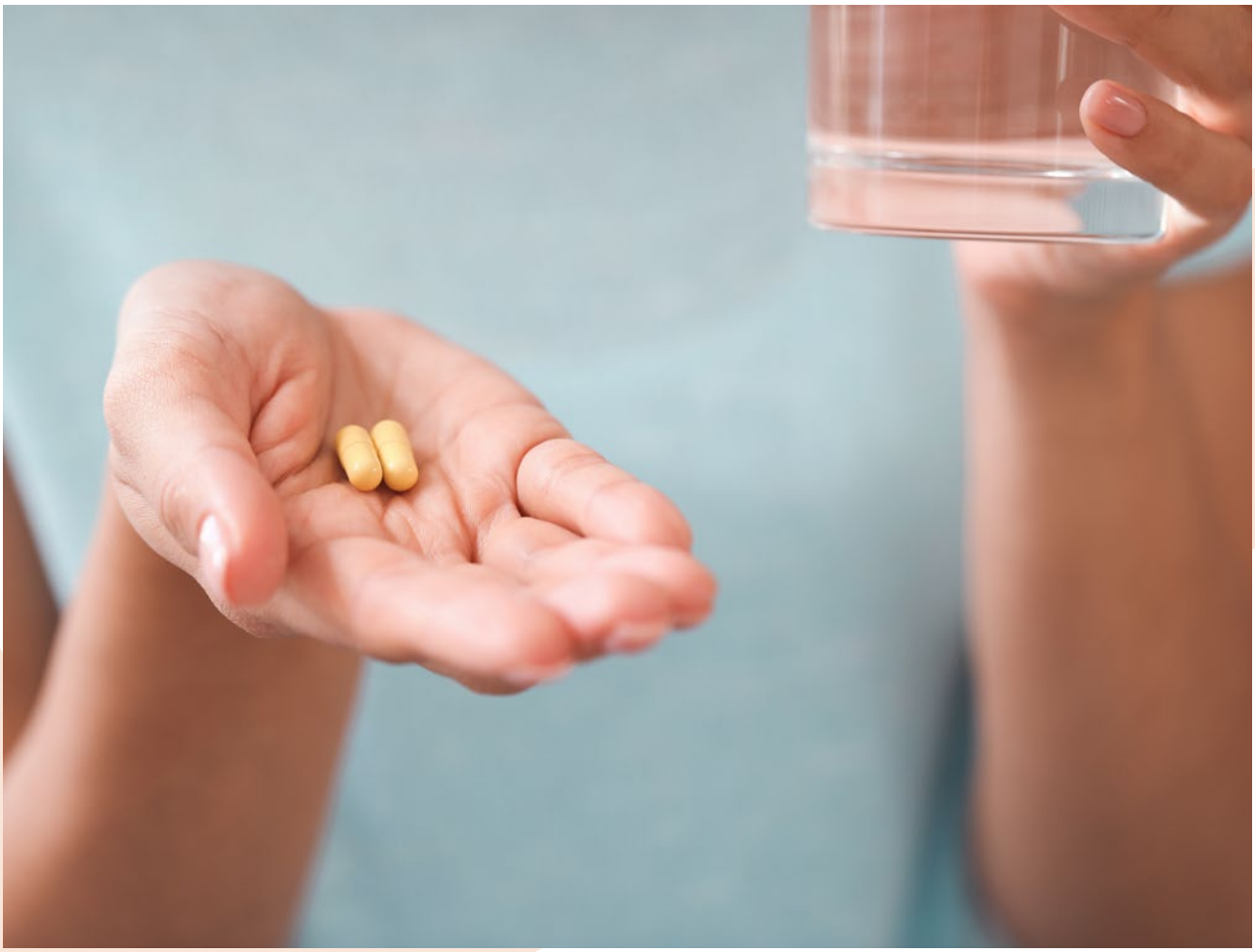
The definition of difficult-to-treat rheumatoid arthritis consists of three criteria agreed upon by a multidisciplinary group of experts. According to van Laar: "It's in a way an arbitrary definition, but it will help us in future clinical trials to define this subgroup." The first criterion is failure to respond to two biological or targeted synthetic (b/ts) DMARDs with different mechanisms of action, after failing conventional DMARD therapy. The second criterion is presence of signs suggestive of active or progressive disease, defined as one or more of the following items: at least moderate disease activity; signs or symptoms suggestive of active disease; inability to taper prednisolone below 7.5 mg; rapid radiographic progression; and rheumatoid arthritis symptoms that are causing a reduction in quality of life. "Not unimportantly, we also felt

that of course the patients and the treating physicians should have a stake in labelling a patient as difficult to treat," added van Laar. Therefore, the third criterion is that the management of symptoms should be perceived as problematic by the rheumatologist or the patient. Using this definition, the proportion of patients meeting the criteria for difficult-to-treat rheumatoid arthritis will range from 5% to 20%. "I think we've kind of overlooked this population because we are focused so much on treating patients very early," summarised van Laar.

MANAGEMENT OF DIFFICULT-TO-TREAT RHEUMATOID ARTHRITIS

Van Laar spoke about points to consider for the management of difficult-to-treat rheumatoid arthritis. If a patient has a presumed diagnosis of difficult-to-treat rheumatoid arthritis, the possibility of misdiagnosis or the presence of a coexistent mimicking disease should be considered as a first step. "I still see, once in a while, patients referred to me with difficult-to-treat rheumatoid arthritis who don't have difficult-to-treat rheumatoid arthritis, but for example crystal arthropathy, which can also be polyarticular," revealed van Laar. Secondly, when there is doubt on the presence of inflammatory activity based on clinical assessment and composite indices, an ultrasound may be considered. It is also important that composite indices and clinical evaluation are interpreted with caution in the presence of comorbidities, especially obesity and fibromyalgia, because these may directly heighten inflammatory activity, or overestimate disease activity.

"Van Laar began by discussing the case of a 60-year-old female with obesity who was diagnosed with rheumatoid arthritis 15 years earlier."



"We need to involve the patient," said van Laar. For this reason, treatment adherence should be discussed and optimised within the process of shared decision making. After failure of a second or subsequent b/tsDMARD, and particularly after two TNF inhibitor failures, treatment with a b/tsDMARD with a different target should be considered. If a third or subsequent b/tsDMARD is being considered, the maximum dose, as found effective and safe in appropriate testing, should be used. "It's understandable that in these patients, you are more cautious in prescribing the optimal dose, but [...] if there's no contraindications, for example in terms of kidney function, go for the optimal, high dose," van Laar commented.

Comorbidities that impact quality of life, either independently or by limiting rheumatoid arthritis treatment options, should be carefully considered and managed. In patients with concomitant hepatitis B or hepatitis C viral infection, b/tsDMARDs can be used, and concomitant antiviral prophylaxis or treatment should be considered in close collaboration with hepatologists. "I think the management of difficult-to-treat rheumatoid arthritis patients increasingly depends on close collaboration with other specialities, including the lung specialist, gastroenterologist, nephrologist, or infectious disease expert," emphasised van Laar. In addition to pharmacological treatment, nonpharmacological interventions should be considered to optimise management of functional disability, pain, and fatigue. "Again, the level of evidence is relatively low, like for the other points, but the level of agreement for all these points was very high," stated van Laar.

Appropriate education and support should be offered to patients to directly inform their choices of treatment goals and management. Rheumatologists should also consider offering self-management programmes, relevant education, and psychological interventions to optimise a patient's ability to manage their disease confidently.

DIFFICULT-TO-TREAT RHEUMATOID ARTHRITIS: A CASE

To finish, van Laar returned to the patient case he presented in the beginning. Although the criteria were not available at the time, this patient fulfilled the definition of difficult-to-treat rheumatoid arthritis. According to van Laar, the key strategic decision was to invest time in the patient.

Initially, the issue of prednisolone was discussed, which the patient had had been using as an analgesic, upping the dose when they were in more pain. "The key thing is not to change the dose from what you have been prescribed," explained van Laar. He added: "This lady had gained a lot of weight from prednisolone; I think 20 kg. She wasn't obese before she had rheumatoid arthritis." Later on, it may be possible to taper the dose.

Secondly, van Laar and his team convinced the patient that methotrexate was the anchor drug for rheumatoid arthritis treatment. This was necessary because the patient had developed nausea from methotrexate, and was reluctant to take it again. The patient was started on the lowest dose of 2.5 mg per week, and reassured that this would not be associated with any side effects. Van Laar described this as the placebo effect of the doctor. Over time, the dose of methotrexate was slowly increased to the highest tolerable dose. Ultimately, the patient was able to tolerate 10 mg per week, which van Laar was "quite happy with" and considered to be a "nice background dose." Finally, one of the new JAK inhibitors was introduced.

> **"To conclude, van Laar shared three take home messages."**

Within 2–3 months, the patient had achieved a state of low disease activity, and was able to return to work and exercise. "Having an overall look at the patient will help you improve the management," summarised van Laar.

CONCLUSION

To conclude, van Laar shared three take home messages: difficult-to-treat rheumatoid arthritis, as defined by the EULAR task force, is not uncommon; the management of patients with difficult-to-treat disease requires an holistic approach; and the condition is not necessarily endstage or irreversible. ●

Abstract Highlights

The following highlights spotlight several fascinating and timely abstracts presented at the European Alliance of Associations for Rheumatology (EULAR) 2022 Congress, covering topics such as autoimmune rheumatic diseases and severe COVID-19 outcomes and lumbar mechanical tractions in radicular pain of discus origin.

Tocilizumab as an Alternative Treatment for Systematic Sclerosis

INTERSTITIAL lung disease (ILD) is the most frequent presentation of systemic sclerosis (SSc), a low-prevalence autoimmune disease with generally heterogenous presentation. SSc also frequently presents with skin involvement and is often treated with classic immunosuppressive therapy used in fibrosis treatment. However, in 2021 the U.S. Food and Drug Administration (FDA) approved the first biologic therapy for ILD-SSc, tocilizumab (TCZ), based on the outcomes from two clinical trials.

Researchers from the Clinical University Hospital, Santiago de Compostela, Spain, aimed to assess the efficacy of TCZ in SSC with both ILD and skin involvement. The study was based on a literature review using Medline, Embase, Cochrane Library, and the Web of Science databases, including clinical trials, observational studies, and case series. A random-effects model meta-analysis was carried out to evaluate TCZ efficacy where comparable measures were found. This method identified 1,036 articles with 13 studies eligible for review.

The effect of TCZ in SSc skin involvement was measured by the modified Rodnan Skin Score (mRSS) and the results found a non-significant improvement in mRSS and a change in mean mRSS (odds ratio: 1.22 [0.72–2.01]; p=0.43 and standardised mean difference: -0.69 [-1.48–0.10]; p=0.09, respectively). However, for ILD-SSc, a significant worsening of forced vital capacity was reported in patients treated with TCZ (odds ratio: 0.45 [0.23-0.86]; p=0.02).

"Researchers from the Clinical University Hospital, Santiago de Compostela, Spain, aimed to assess the efficacy of TCZ in SSC with both ILD and skin involvement."

The researchers concluded from this review and meta-analysis that TCZ could delay the worsening of ILD-SSc and should be considered as a therapeutic alternative to classical immunosuppressive therapy. The authors emphasised the necessity of addition research in this topic for a better understanding of the disease and the implication of TCZ in other organ impairment. ●

Autoimmune Rheumatic Diseases and Severe COVID-19 Outcomes

THE SURGE of COVID-19 has impacted the population globally. However, individuals with autoimmune rheumatic diseases (ARD) could have an increased risk of developing severe outcomes of the disease.

Researchers from Vancouver, Canada, carried out a population-based cohort study, aiming to assess the risk of severe COVID-19 outcomes in patients with ARDs compared with a matched population without ARDs. The factors considered included the risk of COVID-19 hospitalisation, intensive care unit (ICU) admission, and mortality with a primary International Classification of Diseases (ICD) code, indicating COVID-19. The researchers used datasets from British Columbia, Canada, from February 2020 to August 2021, and obtained data from patients with ARDs including rheumatoid arthritis, psoriasis/psoriatic arthritis, and systemic lupus erythematosus.

The selected individuals were population matched in a 1:5 ratio to a general population with a positive COVID-19 test, based on age, sex, health authority, and the time of COVID-19 contraction. The study also used a conditional logistic regression model to adjust for several factors including socioeconomic status, hypertension, rural address, and Charlson Comorbidity Index (CCI) before carrying out multiple COVID-19 tests.

Results showed that patients with ARDs had a significantly increased risk of COVID-19-related hospitalisation, with an adjusted odds ratio (aOR) of 1.03, with the group at the greatest risk being individuals with adult systemic vasculitides. For patients with ARDs, the risk of ICU admission revealed an aOR of 1.30, indicating an increased risk. Patients with ankylosing spondylitis had the greatest risk within the ARD population of being admitted to ICU. The risk of COVID-19-specific mortality also presented with a significant increase within the ARD group, with an aOR of 1.24. Individuals with the greatest risk were also those with ankylosing spondylitis.

> **"Early diagnosis and treatment of patients within this group should also be prioritised by healthcare professionals."**

Overall, this study shows a clear correlation between ARDs and the risk of severe COVID-19 outcomes, with this impact varying between specific diseases. The study authors recommended strategies to reduce this risk, including the severe acute respiratory syndrome coronavirus 2 booster vaccination. Early diagnosis and treatment of patients within this group should also be prioritised by healthcare professionals. ●

Lumbar Mechanical Traction Proves Superior

LUMBOSCIATIC pain is currently treated with non-steroidal anti-inflammatory drugs, analgesics, and physical therapy. Lumbar mechanical tractions do not have a clearly identified place in the treatment of lumbosciatic pain of discal origin, and literature studies have failed to show significant efficiency in lumbar mechanical tractions. E. Bernhard, Rheumatology Unit, Centre Hospitalier Universitaire (CHU) de Reims, Maison Blanche Hospital, France, presented the findings of a monocentric interventional prospective study, which aimed to demonstrate the superiority of lumbar mechanical traction against standard treatment alone, at EULAR 2022.

From 2013 to 2021, Bernhard and colleagues recruited 428 patients with lumboradicular pain with concordant discal hernia, but who were also naïve of lumbar surgery. They were separated into two groups depending on how they would be treated. One was the medical group (n=210), where patients received the standard treatment and a minimum of two epidural infiltrations. The other was the traction group (n=209), where patients received the standard treatment along with at least three lumbar mechanical traction sessions.

The amount of pain that the patients were in was tested at baseline, 1 month, and 3 months. Treatment was considered effective if a patient's pain decreased by 25% from baseline to 1 month. Pain was assessed through an analogue scale on lumbar and radicular localisation, with the superiority analysis performed by the chi-square test.

> **"Lumbar mechanical tractions do not have a clearly identified place in the treatment of lumbosciatic pain of discal origin"**

Of the 428 patients recruited for this randomised controlled study, 11 patients had missing data; however, 205 patients (49.52%) presented with right lumboradiculalgia and 209 (50.48%) with left, which were primarily in L5 (172 [41.0%]) or S1 (207 [50.0%]).

Before the 1-month follow-up, 20 patients (5%) had to be operated on. However, a total of 212 patients had a reduction in pain at 1 month: 117 (31%) in the traction group and 95 (25%) in the medical group. Therefore, patients who were also treated with lumbar mechanical traction had a significant reduction in pain (p=0.036) compared with those who received standard treatment alone. ●

T Cell Response After COVID-19 Vaccine in Systemic Autoimmune Disorders

RESEARCHERS have discovered that T cell response in patients with systemic autoimmune disorders currently receiving early rituximab treatment or belimumab is unimpaired by COVID-19 vaccination.

Patients diagnosed with autoimmune disorders have an increased risk compared with the general population of contracting infection and of developing serious complications. Infections in this patient group can be reactivated and the disease itself can become worsened in consequence. Vaccination has long been seen as the main tool to prevent infectious diseases, and it must be stressed that vaccination is an important measure that is both safe and beneficial for this patient cohort.

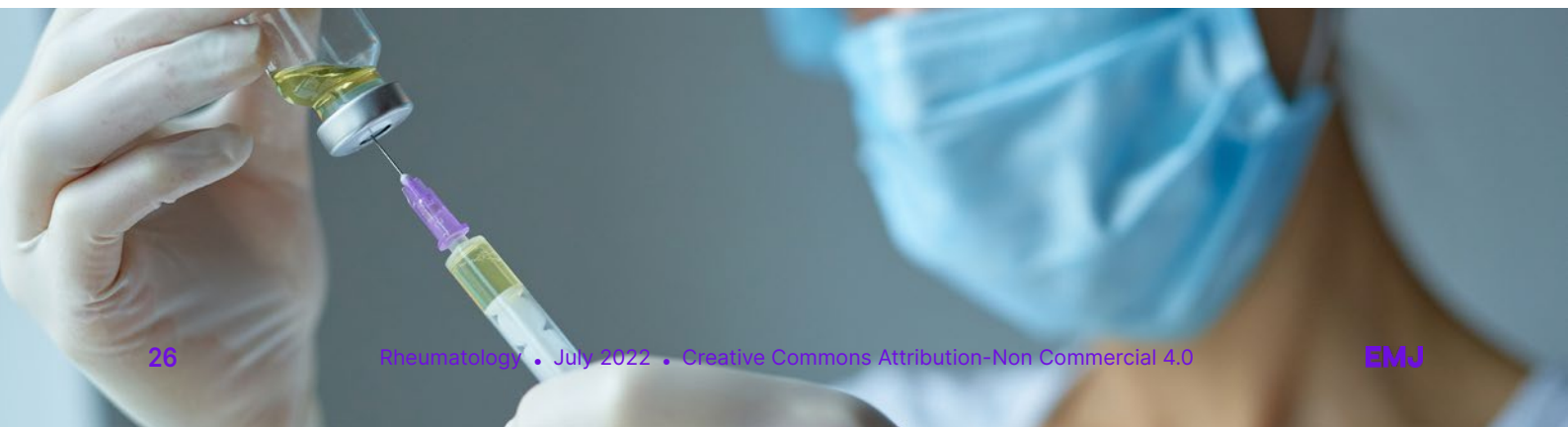
However, drugs that suppress the immune system and are used to treat rheumatic diseases may impair the patient response to vaccines. This is particularly true of those drugs which directly target B or T cells.

The study, led by G. De Marchi, Division of Rheumatology, Department of Medicine, Udine, Italy, aimed to explore B and T cell-mediated immune response to messanger RNA vaccination against COVID-19 in patients with systemic autoimmune diseases, including systemic connective tissue diseases or vasculitis. The study population included 28 patients who were either early or continuously treated with B cell-targeting therapies, rituximab (n=11) or belimumab (n=17), and 13 controls matched for age and sex. No patients presented antibodies to severe acute respiratory syndrome coronavirus 2 related to prior viral contact and all tested negative at each monthly control.

All study participants were given messanger RNA vaccines, and were tested between 3 and 4 weeks following complete vaccination. All patients on rituximab began vaccination within 5 months from their last infusion and all but one of these were B cell depleted. Detectable anti-severe acute respiratory syndrome coronavirus 2 antibodies were found in one of 11 patients on rituximab and 16 of 17 patients receiving belimumab. Anti-receptor binding domain antibodies were discovered in all but one patient in the belimumab subgroup.

> **"It must be stressed that vaccination is an important measure which is both safe and beneficial for this patient cohort."**

The study concluded that therapies that target B cells do not prevent the benefits of vaccination against COVID-19, as cellular immunity can occur even in the absence of circulating B cells. The immunogenicity following COVID-19 vaccination in patients with systemic autoimmune disorders who receive belimumab is supported. However, those patients who receive a lower vaccine response may remain at higher risk of infection. ●



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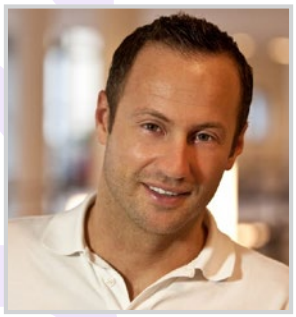
Congress Interviews



Xenofon Baraliakos

Professor of Internal Medicine and Rheumatology, Ruhr-University Bochum, Germany; Treasurer of EULAR

Q1 What inspired you to pursue a career in rheumatology?

Well, there are different arguments for pursuing a career in rheumatology. There are people who want to work more clinically and there are people who want to work more scientifically. There are also individuals who want a combination of both. The interesting thing for me, which was the main reason I went into rheumatology, is that you can combine both based on your interests and on the way that the set-up is offering opportunities. It is always the case that you can easily work either clinically or scientifically or both. You can also get ideas from the clinic to go into scientific work. I think that this is a very interesting field to work in because it's not always the same. It changes scenery and remains challenging. It is also very interesting to think about cases and then put them into a scientific discussion or question that doesn't necessarily have to be answered by a study, but can also be answered in daily practice, by tools such as objective and clinical examinations.

Q2 What is the most rewarding part of your job as a professor for internal medicine and rheumatology?

The most rewarding part of the professorship for internal medicine and rheumatology is the scientific work that I do. I work in clinics as well, and the most rewarding thing is to see questions arising from clinical work, bringing these into scientific questions that can be answered by studies, and also bringing this knowledge back to the patient, where again we can answer clinical questions through evidence.

Q3 How have you seen the field of rheumatology change over the years in terms of advancements to the technology used?

I have been following this field for more than 20 years and there have been huge advancements. Advancements in terms of treatment of the patients, as well as advancements in terms of imaging tools and laboratory findings. The whole field has evolved through clinical work by having a clear understanding of the patients, and also by how to apply the proper treatment for each patient type.

Q4 With an impressive collection of published articles and a high h-index of 70, what do you think makes your publications well-received, and have you noticed any gaps in the literature?

I believe that the scientific part of my work, and that of my collaborators, has been that we've answered clinical questions. This closes gaps in a single question but also in larger fields. Obviously, this may lead to well-received publications in the field. What

still surprises me a lot is that we do not run out of questions, and we do not run out of ideas. It seems that there is still lots to be done and many questions to be answered in order to close any gaps in the field.

Q5 As a member of the European League Against Rheumatism (EULAR), what are your responsibilities?

My responsibility, always as part of a team, is to help ensure a smooth running of the congress, and to give my input into how we could possibly allocate topics and improve the scientific content. There is also a congress committee, which is mainly working for this reason. As a EULAR family, we aim for the best scientific and clinical experience at the congress.

> **"The collaboration between those pillars is also a way to address gaps, as I mentioned before, looking at them from different angles."**

Q6 How do you think that the EULAR Congress benefits the rheumatology community and patients?

Well, this is a very relevant queston because at the congress we have clinical scientific sessions; we have basic scientific sessions; and we have the involvement of the other pillars of EULAR, including patient and

healthcare professioanal societies. Overall, it's a very nice mixture. The collaboration between these pillars is a way to address knowledge gaps by looking at them from different angles. Importantly, what we hear and learn can be implemented in daily practice after the congress.

Q7 What are the most exciting changes that have been made to the scientific programme for EULAR 2022 compared with EULAR 2021?

It is exciting to see that we don't run out of questions. There are many different topics that have been exciting for me to look into, both in diagnosis and diagnostics but also in treatment and patient experience. This year at EULAR, we have also seen updates to treatment recommendations. I believe we have a very unique scientific programme that will set the stage for different kinds of discussions in the future.

Q8 In the recent, double-blind randomised Phase III MAXIMISE trial, you reported on the effects of secukinumab in patients with psoriatic arthritis and axial manifestations. What were the take-home messages from this study?

This was a study that was the first of its kind, addressing the question of treatment efficacy of a biologic in patients with so-called axial psoriatic arthritis. We applied the outcomes for axial symptoms in patients with psoriatic arthritis who had axial symptoms as well. We found that they were very responsive and had a fast response to their treatment with secukinumab. Subsequent analysis has also identified predictors of which patients are going to report a better or worse outcome, although the vast majority of patients responded very well anyway. The even better responders were those who were in the peripheral disease of psoriatic arthritis who not only had arthritis but also nail involvement.

Q9 Finally, are there any innovations on the horizon in the field of rheumatology that you think are particularly noteworthy?

We have a plethora of innovations and interest in many different diagnoses and indications. For my scientific area, which is axial arthritis and psoriatic arthritis, I believe the most interesting clinically-oriented innovation is that we are now learning how to better apply treatment to specific patients. Patient-tailored treatment, together with the new modes of action that we have, is something that we shall follow up during subsequent congresses.

EMJ Interviews

Jeffrey A. Sparks and Lorinda Chung spoke about their careers and influential research, as well as the impact of the pandemic on their practice. The experts also shared insights into new and innovative developments in the field.

Featuring: Jeffrey A. Sparks and Lorinda Chung

Jeffrey A. Sparks

Associate Physician, Brigham and Women's Hospital, Boston, Massachusetts, USA; Assistant Professor of Medicine, Harvard Medical School, Boston, Massachusetts, USA

Q1 What led you to pursue a career in rheumatology and population science?

I confess that serendipity was a main driver of my career path. In college, I was a physics major with an interest in humanities. Medical school seemed like a great way to meld my interest in science and people, while also delaying an ultimate career decision. I entered medical school vaguely thinking that radiology may be interesting, but I quickly figured out that I wanted to be ordering the imaging test as an internal medicine physician. During residency, I first became exposed to clinical research. I never found bench research enticing, so I thought it was really exciting that patient and population level data could be used to ask and answer questions of immediate clinical relevance. I became interested in rheumatology at the tail end of residency at Washington University in St. Louis, Missouri, USA. After deciding I wanted to give clinical research in rheumatology a try, I was lucky enough to match at Brigham and Women's Hospital, Boston, Massachusetts, USA. I hit the lottery with a great mentor, Elizabeth Karlson, in a great research section, the Section of Clinical Sciences, led by Daniel Solomon. I also completed a Master of Medical Sciences degree at Harvard Medical School, Boston, Massachusetts, USA to obtain training in epidemiologic and patient-oriented research. Papers in fellowship led to grants to support my junior faculty salary, which led to more papers and grants. All in the blink of an eye!

Q2 How does your involvement as a member of an editorial board contribute to increased awareness in rheumatology?

Editorial boards have been extremely helpful to help hone my science, and understand the state-of-the-art in methods and topics. Peer reviewing and editorial roles have really crystallised how to structure my papers to efficiently tell the story of the study. However, the process can be humbling, and sometimes luck is just not on your side. As in other specialties, the number of journals and paper submissions have

grown in recent years. The quality of papers has really helped visibility of rheumatology and attracted talented trainees to our field. I think trainees see the many opportunities that rheumatology offers to study the immune system and musculoskeletal health.

Q3 Over the years, you have received many research awards. What is the moment in your career that you are most proud of, and why?

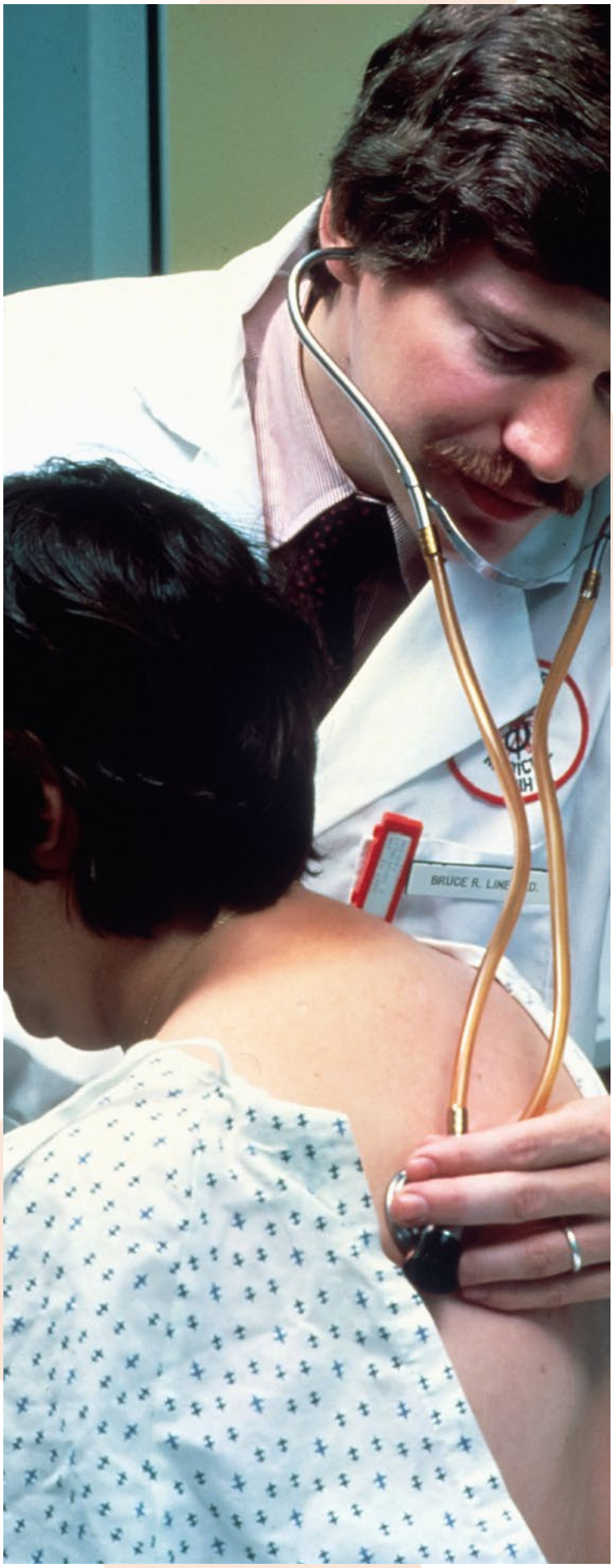
As a physician–scientist, it sometimes can feel that the clinical and research sides of my work live in distinct phases. One of the proudest moments was the first time that a patient travelled to see me in clinic solely based on a research paper (ironically, one of my least cited), and thanked me for doing this research that helped them. I genuinely had not considered that this moment could even happen, so I felt immediate gratitude and inspiration to pursue clinical research.

> **"One of the proudest moments was the first time that a patient travelled to see me in clinic solely based on a research paper."**

Q4 What were your responsibilities as the chair of the American College of Rheumatology (ACR)'s Early Career Investigators Subcommittee?

This is a fantastic ACR committee for early career investigators that I was lucky to have chaired. I was able to meet and interact with leaders in the ACR who will be lifelong colleagues and friends.

We organised the annual Rheumatology Research Workshop (RRW). At the RRW, trainees submit abstracts and attend a 1.5-day conference about career development and honing their project. This is concurrent with other events from the ACR and the Rheumatology Research Foundation, so it is a great networking event with leaders. During my tenure, we also designed and launched a mentorship program for adult rheumatology trainees called CARMA (Creating Adult Rheumatology Mentorship in Academia) that has been very successful. We also organised a session at the ACR Annual Meeting called Meet the Funders, where trainees can meet with representatives of organisations that fund rheumatology research.



Q5 COVID-19 has impacted healthcare worldwide; how has the pandemic affected your consultations, and has there been a prevalence of a particular rheumatic condition during COVID-19?

Virtual care has certainly been the biggest change with clinical care during the pandemic. This has mostly provided greater flexibility to patients. However, sometimes it can be frustrating that a true assessment cannot happen over video (and certainly not labs, imaging, or other tests). As far as specific conditions go, I was most surprised at how many had delayed seeking care as we were initially seeing patients in person. I feel like we are just now getting to a more usual flow of patients related to their symptom onset and clinical evaluation. Of course, integrating specifics about COVID-19 infection and vaccination has added more complexity to every interaction. There are certainly some patients where COVID-19 infection seems to have been a trigger in their clinical presentation.

Q6 You have been involved in many fascinating clinical trials and research projects for rheumatic

arthritis (RA). In one such study, you assessed obesity and RA risk. Could you share a summary of the effect obesity has on RA risk?

Similar to other groups, we have been investigating the impact of metabolic factors on RA risk. This includes the complex relationships between weight, dietary intake, and physical activity. We found that obesity was associated with increased RA risk compared with normal BMI. Similarly, those who were more physically active were less likely to develop RA. We also showed that high-quality diet and anti-inflammatory dietary patterns were associated with lower RA risk. Two of our early studies showed that weight loss either from bariatric surgery or non-surgical measures were associated with improved RA disease activity.

While more work needs to be done, most data show that obesity could contribute to systemic inflammation that could eventually lead to RA. Among those with RA, obesity may also be a factor in disease activity.

Q7 Are there new clinical trials or noteworthy research projects on the horizon that you are currently involved in?

We recently launched a multicentre study investigating lung health in early RA called SAIL-RA. This includes Brigham and Women's Hospital; Massachusetts General Hospital; the University of Colorado, Denver, USA; and the University of Michigan, Ann Arbor, USA. We are enrolling patients with RA, newly diagnosed with RA, and following them for 2 years with study visits every 6 months to gather data on RA and lung health that includes high-resolution chest CT imaging, pulmonary function tests, 6-minute walk tests, surveys, physical examination, and blood banking. This has been the culmination of years of research to investigate what we termed the 'respiratory burden of RA'. I am extremely thankful that the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) chose to fund SAIL-RA. We are planning for interim results in the next year.

> "These results suggest that risk for developing RA may be modifiable."

Q8 What were the key take-home messages from the recent article that you authored, entitled 'Association of Healthy Lifestyle Behaviours and the Risk of Developing Rheumatoid Arthritis among Women'?

That study was led by Jill Hahn and Karen Costenbader, and was the culmination of many years of RA research using the Nurses' Health Studies. We have identified many risk factors for RA using prospective data from nearly 250,000 females, some of who have been followed for over 40 years. We have been identifying incident RA cases over the last few decades along with many other investigators, including Elizabeth Karlson. This study investigated a summary score of five behaviours that were previously linked to RA risk: smoking, alcohol consumption (moderate drinking associated with lower risk), BMI, physical activity, and diet. We found that higher values on the Healthy Lifestyle Index (HLI) score were strongly associated with lower RA risk. Compared to those without healthy behaviours, those who adhered to all healthy measures were associated with a 68% lower risk of developing RA. These results suggest that risk for developing RA may be modifiable.

Lorinda Chung

Professor of Medicine (Immunology and Rheumatology) and Dermatology, Stanford University of Medicine, California, USA.

Q1 How did your education bring you to where you are today and what motivated you to study medicine, in particular rheumatology?

My father is a physician and served as an inspiration for me and my three older sisters to go into medicine. Having attended undergraduate and medical school on the East Coast and in the Midwest, respectively, I always wanted to move to California, USA. I matched at Stanford for my internal medicine residency and fell in love with the school and the area. During my internship, my oldest sister developed a connective tissue disease, which has since evolved into systemic sclerosis. She has been my driving force for pursuing a career in rheumatology with a focus on systemic sclerosis.

Q2 As an educator, where can we expect to see your focus lie in the coming years?

My favourite part of my job is working with and mentoring trainees and junior faculty. I have mentored many residents and fellows, assisting them with attaining their career goals and initiating scleroderma programmes of their own. In the coming years, I hope to provide mentorship to visiting junior faculty from other institutions, particularly international institutions, and to guide them in the development of their own scleroderma centres or dermatology–rheumatology programmes.

Q3 Could you briefly detail how you initiated and developed the Stanford Scleroderma Program?

During my rheumatology fellowship, I partnered with David Fiorentino, a Professor of Dermatology at Stanford, to develop one of the nation's first rheumatologic dermatology clinics. With my personal interest in systemic sclerosis, our clinic quickly attracted this patient population. We applied for funding support from the Scleroderma Research Foundation (SRF), and their continued support of our centre since 2009 has enabled us to expand and to develop key national and international research collaborations.

Q4 What is one lesson that you have learnt from leading teams of over 15 clinicians and researchers?

Everyone has something important to contribute. Therefore, it is paramount to make sure that everyone's voices are heard and that their contributions are acknowledged.

Q5 Are there any noteworthy clinical trial designs you are currently working on?

I serve as an advisor for several industry sponsors and am assisting with protocol development for clinical trials in systemic sclerosis and Raynaud's phenomenon, but this information is confidential.

"I have mentored many residents and fellows, assisting them with attaining their career goals and initiating scleroderma programmes of their own."

Q6 What is your responsibility as the Director of the Women's Rheumatology Clinic at the Palo Alto Veteran Affairs (VA) Health Care System?

I developed the Women's Rheumatology Clinic at the Palo Alto VA in 2009 to cater to the growing population of female veterans. This clinic, in combination with other women's health subspecialty clinics, serves to provide continuity of care and comprehensive medical care to female veterans, with a focus on their particular needs.

Q7 Is there a rheumatic condition that you are particularly interested in and that you believe has a lack of awareness?

In addition to systemic sclerosis, David Fiorentino and I focus our clinical and research efforts on a rare autoimmune condition called dermatomyositis. We are particularly interested in understanding the pathogenesis of this disease and the role that autoantibodies and inflammatory signalling molecules play in patient presentation and prognosis.

Q8 Over your career, you have received over 15 awards. What accomplishments are you most proud of?

As I mentioned previously, serving as a mentor for trainees is the most fulfilling aspect of my job, and I received the Teaching Award from the Department of Medicine at Stanford in both 2014 and 2019. I was also nominated by several former mentees for the American College of Rheumatology (ACR) Excellence in Investigative Mentoring Award in 2020. Although I was not awarded that year, it was an incredible honour to be nominated by my former mentees.

Q9 If you were to change one thing about your field, what would it be and why?

That we could cure patients of their autoimmune diseases. Although we have many effective therapies for patients with rheumatic diseases, we still do not have any cures, and most of our patients must continue to live with symptoms related to their chronic diseases.

Q10 Are there any innovations on the horizon in the field of rheumatology that you think are particularly noteworthy?

Chimeric antigen receptor T cells targeting B cell surface antigens are being explored as a novel treatment strategy in autoimmune diseases. This strategy holds promise to induce sustained remission of autoimmune diseases, and clinical trials for this are currently being initiated.

Multisystem Inflammatory Syndrome in Children and Kawasaki Disease: A Clinical Conundrum

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in general leads to a mild disease in children, but a rare yet serious complication of multisystem inflammatory syndrome in children (MIS-C) has been reported.[1] MIS-C cases are on the rise during the COVID-19 pandemic, and clinical features overlap between MIS-C and an already well-known clinical entity in children: Kawasaki disease (KD). Both KD and MIS-C are diagnoses of exclusion, and can present with acute fever and increased inflammatory markers without any other potential aetiology.[2] Despite the overlap in clinical presentation, there are some differentiating features that could help establish an accurate diagnosis and appropriate management, which are highlighted in this article.

CASE DEFINITIONS

The Centers for Disease Control and Prevention (CDC) case definition of MIS-C is an individual aged <21 years presenting with fever of >38.0 °C lasting >24 hours, laboratory evidence of inflammation, clinically severe illness requiring hospitalisation, with multisystem (>2) organ involvement; no alternative plausible diagnoses; and positive result for current or recent SARS-CoV-2 infection by reverse transcriptase-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms. Laboratory evidence of inflammation includes, but is not limited to, one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or IL-6; neutrophilia; lymphopenia; and hypoalbuminaemia.[3] The World Health Organization (WHO) case definition of MIS-C differs from that of CDC by age criteria of 0–19 years and fever >3 days.[4]

KD is a vasculitis of medium-sized blood vessels that presents as an acute illness in a patient with a fever of ≥5 days duration and the presence of ≥four of the five principal clinical features that include: erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa; bilateral bulbar conjunctival injection with no

exudate; maculopapular, diffuse erythroderma, or erythema multiforme-like rash; erythema and oedema of the hands and feet in the acute phase, and/or periungual desquamation in the subacute phase; and cervical lymphadenopathy (≥1.5 cm diameter). Patients whose illness does not meet the CDC case definition but who have fever and coronary artery abnormalities are classified as having atypical or incomplete KD.[5]

CLINICAL FEATURES

KD often affects young children <5 years and is more common in the Asian population.[5] However, for MIS-C, the average age of presentation is 9–11 years, and it is more common in children from Black and Hispanic backgrounds, which could be because of increased incidence of SARS-CoV-2 infection in these subgroups.[6,7] Seasonal variations are noted in KD, and it is more common in winter and spring. Temporal association between MIS-C cases and an increase in the number of SARS-CoV-2 cases has been noted since the beginning of the pandemic; MIS-C usually presents 4–5 weeks after SARS-CoV-2 infection, which is itself usually mild.[2,6-8] Differentiation can be difficult based on clinical features alone, as both KD and MIS-C can present with fever, increased inflammatory markers, and mucocutaneous manifestations. However, in MIS-C, cardiac markers such as B-type natriuretic peptide and troponin are increased, with associated thrombopenia, leukopenia, and lymphopenia; whereas, thrombocytosis is common in KD. Coagulopathy, gastrointestinal symptoms, neurocognitive symptoms, and diastolic dysfunction with cardiogenic shock are more common in patients with MIS-C compared to KD.[1,2]

Both KD and MIS-C can have cardiac sequelae, and KD is the most common cause of acquired heart disease in paediatric populations across the globe. Coronary aneurysm can be a potential complication in both KD and MIS-C. Left ventricular dysfunction is the most common cardiac complication of MIS-C, followed by coronary artery aneurysm and conduction abnormalities, which emphasises the need for different management and follow-up strategies based on cardiac involvement.[7,8] Echocardiogram is recommended to screen coronary aneurysms and to assess ventricular dysfunction during the acute illness. Development of new coronary artery aneurysms can be seen in the convalescent phase of illness and serial follow-up echocardiograms at 1–2 weeks and then at 4–6 weeks are needed, even in patients with no cardiac abnormalities in the acute phase of illness.[7] In addition, serial monitoring with B-type natriuretic peptide, troponin, and ECG is also recommended.

MANAGEMENT

Similarities and dissimilarities exist in management as well. Intravenous Ig (IVIG) with high-dose aspirin is the recommended first-line treatment of KD.[5] Infliximab, cyclosporine, glucocorticoids, and plasmapheresis have been reported to be successful in treating IVIG-resistant cases. Antiplatelet and anticoagulation therapies should be considered for large (≥8 mm) and/or persistent coronary aneurysms. So far, there are no standardised treatment guidelines developed for MIS-C management, and low-dose aspirin is recommended to decrease the risk of thrombosis; long-term use of aspirin is tailored according to thrombophilic risk factors. Inotropic agents are used in MIS-C management due to diastolic dysfunction. Some observational studies have reported favourable outcomes with glucocorticoids in addition to IVIG as initial treatment, when compared to IVIG alone.[7-9] However, to date, there are no available clinical trial data comparing these two treatment modalities. Clinical trials comparing infliximab, a TNF inhibitor, as an initial treatment along with IVIG compared to IVIG alone are emerging, and preliminary results suggest that patients treated with combination therapy are less likely to require additional therapy with vasoactive agents, had decreased length of intensive care unit stay, decreased development of left ventricular dysfunction, and more rapid decline in C-reactive protein levels.[10] However, the data available so far are limited to the management of the acute phase of the disease, and no data are available regarding the long-term consequences of this disease.

The aetiology of KD remains unknown, and no preventative strategies are known. However, MIS-C is clearly related to SARS-CoV-2, and vaccinations for SARS-CoV-2 have been

approved for children aged ≥5 years in many countries.[11] Emerging research suggests that children as young as 6 months old might need to receive their own vaccine, as antibodies acquired passively by placental transport start declining at 6 months of age; there are ongoing trials regarding the safety and efficacy of SARS-CoV-2 vaccine in children 6 months and above.[12] Further, recent studies have revealed that MIS-C is less common in children aged 12–18 years who were vaccinated with two doses of BNT162b2, and MIS-C could be a vaccine-preventable disease.[13]

CONCLUSION

KD and MIS-C have clinically overlapping features, but are different entities (Table 1). Early diagnosis and management are crucial for successful and timely management of both these conditions and follow-up. There is no standardised treatment available for MIS-C at this time, and further clinical trials are needed to compare the safety and efficacy of the various available treatment regimens, along with the effect on long-term outcomes. There is growing evidence that the incidence of MIS-C is low in fully vaccinated children, which further emphasises the importance of vaccination in children.

Table 1: Comparison between multisystem inflammatory syndrome in children and Kawasaki disease.

	Kawasaki Disease	MIS-C
Aetiology	Unknown	Preceding SARS-CoV-2 infection or exposure in the last 4 weeks
Diagnosis	Fever ≥5 days with four out of five of: • Polymorphous rash • Oral mucosa changes • Extremities changes • Cervical lymphadenopathy ≥1.5 cm • Non-exudative bulbar conjunctivitis	• Fever ≥1 day • Laboratory evidence of inflammation • Two or more organ system involvement (gastrointestinal, cardiovascular, renal, neurological, haematological or cutaneous) requiring hospitalisation
Age	<5 years	8-12 years
Race	More common in Asian population	More common in Black and Hispanic populations
Laboratory findings	Elevated inflammatory markers • CRP • ESR Haematological • Thrombocytosis • Anaemia Others • Elevated liver function tests • Elevated D-dimer	Elevated inflammatory markers • CRP • ESR • Ferritin • Procalcitonin Haematological • Neutrophilia • Lymphopenia • Thrombocytopenia Coagulopathy • Elevated PT/PTT • Elevated D-dimer Cardiac enzymes • Elevated troponin • Elevated BNP

Table 1: Continued.

Complications	Cardiac • Coronary arteritis and aneurysms Multi-organ failure • Uncommon	Cardiac • Ventricular dysfunction and shock (most common) • Arrythmia • Myocarditis • Coronary aneurysm Multi-organ failure • Common
Initial treatment	IVIG with high-dose aspirin	IVIG alone or in combination with glucocorticoids or infliximab*
Follow-up	Echocardiogram • 1–2 weeks • 4–6 weeks	Echocardiogram • 1–2 weeks • 4–6 weeks • Additional follow-up based on cardiac involvement
Outcomes	Fatality: 0.01%	Fatality: 1.4–1.7%

*Based on early clinical trial data.

BNP: B-type natriuretic peptide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IVIG: intravenous Ig; MIS-C: multisystem inflammatory syndrome in children; PT: prothrombin time; PTT: partial thromboplastin time; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

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Immune Relevant Behavioural Interventions: Immunological Evidence as an Integral Measure of Behavioural Interventions for Rheumatic Diseases, a Review of Current Research

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INTRODUCTION

Behavioural interventions and immunologic indicators of health, disease activity, and immune function are discrete subject areas, which have been thoroughly explored in academic research. While many research studies have looked at these subject areas individually, there is less empiric exploration into the relationship between them within rheumatology.[1-4] This is particularly relevant for disorders of the immune system, such as autoimmune diseases, where these subject areas are inextricably related.

Autoimmune disorders have well-established pharmacotherapies and treatment regimens, which address prolonged life, reduce disability, and improve quality of life.[5] However, effective treatment for disorders of the immune system necessitate a multimodal approach that addresses patient-level factors and disease self-management.[6] Behavioural interventions often set out to change these factors in an individual or group as it relates to their physical health. Common elements of behavioural interventions include education, which can be structured or unstructured; experiential learning; and the application of skills learned.[7] In addition to

physical health, behavioural interventions have been employed to reduce the negative effects of adverse psychological states, such as anxiety or depression, by teaching and applying coping skills.[8] The link between the immune system and emotion has been well studied; however, the mechanism of action is complicated, likely due to this complex relationship and variance between psychological states.[9-11]

Other patient-level factors observed to be associated with altered immune function are socioeconomic status, race, gender, and employment.[12-15] Even though these patient-level factors are difficult to directly modify, they are crucial for understanding the connection between overall health and immune function. This is due to the relationship between the individual and their immune system being bidirectional.[16] Not only does an individual's physical health, emotional health, and behaviour affect their immune system, but immune system modulation can lead to changes in emotional well-being and cognition.[11] Given the link between the immune system and patient factors established in research literature, the authors conducted a limited review to provide evidence for the utility of measures of immune function in the assessment of behavioural interventions for rheumatic diseases.

IMMUNE FUNCTION

Many psychological states and environmental factors have connections with the function of an individual's immune system. This is exemplified in the effect that stress can have on the immune system. Psychological stress can shift the Type 1/Type 2 cytokine balance towards Type 2 and result in immune dysregulation. This process is mediated through decreased peripheral blood mononuclear cell interferon-γ and increased IL-10, resulting in reduced host defenses to harmful pathogens.[17] Allostatic load is the deterioration of the body and brain from chronic overactivity or inactivity of physiological systems that aid with adaptations to environmental challenges.[18] Long-term exposure to stressors can lead to a build-up of the physiologic changes that diminish immune response. This wear and tear over time further diminishes the body's ability to fight off infection, and can lead to other risk factors, including obesity, cardiovascular damage, and atrophy of nerve cells in the brain.[19]

Furthermore, the role of cytokines and the immune system may be greater. According to the cytokine hypothesis of depression, pro-inflammatory cytokines may act as neuromodulators and play a critical role in the modulation of depressive disorders. Supporting evidence for this theory includes the correlation between inflammatory autoimmune disorders, such as rheumatoid arthritis and systemic lupus erythematosus (SLE), with depressive symptomatology. Moreover, therapies involving the provision of pro-inflammatory cytokines induce depressive symptoms in some patients. Similar outcomes have also been observed in animal models.[20] While these examples would indicate that the relationship between cytokines and depression is unidirectional, a bidirectional relationship, and the third variable problem have not been ruled out. In addition to depression, a similar relationship has been observed between immune dysfunction and anxiety. This effect is posited to be a result of oxidative stress to immune cells and tissues, which mimics the effects of ageing.[15,21]

The function of the immune system has also been shown to be linked to social support and mental and physical discomfort. Perceived social support is correlated with a greater number of natural killer (NK) cells in the blood. NK cells are cells that combat and kill pathogens in the host.[22] Therefore, individuals with a greater number of NK cells have greater innate immunity and ability to fight off infections.[23] On the other hand, exposure to distressing environments can have a negative effect on the immune system. The perception of pain and the immune system are also linked, such that the perception of pain activates immune cells to mobilise a response to the perceived threat.[24] Pain can subsequently compound the allostatic load that damages the host's immune system over time through the induction of stress and anxiety. This relationship between pain, inflammatory mediators, and associated psychological effects suggests an environment where positive feedback is not only possible, but probable. As a result, behavioural interventions could be directed at any one of these factors with the intent of improving the immune system.

BEHAVIOURAL INTERVENTIONS AND IMMUNE FUNCTION

Behavioural interventions have attempted to address the psychological manifestations and pain that influence this feedback loop. Despite the known relationship between the immune system and modifiable patient factors, measures of the immune system are not prevalent in the domains of rheumatology research. Much of the previous research lies in the study of cancer. For example, McGregor et al.[25] examined the effect of a cognitive-behavioural stress management (CBSM) intervention on females with breast cancer. Outcomes of interest included immune function, emotional well-being, and perceived benefit from the intervention. Females in the CBSM programme perceived greater benefit than those in the comparison group. In addition, at a 3-month follow-up visit, the CBSM group's immune systems had shown greater lymphocyte proliferation. This result was positively correlated with a participant's self-reported benefit from the programme. Similarly, a review conducted by Leucken and Compas[26] argued that there is a wealth of evidence to indicate that behavioural interventions improve emotional and physical factors in patients with cancer, which in turn confer benefit to the immune system by lowering cortisol levels and improving the number of naturally circulating NK cells. Notably though, they were unable to establish a relationship between these variables and improved outcomes, such as life-expectancy.

More recently, a meta-analysis of 76 randomised controlled studies of behavioural interventions in cancer assessed a broad range of immunologic effects. Results were modest but generally positive for the immunologic outcomes assessed. Key conclusions included improving methodological rigor in such trials in order to fully cognise potential intervention benefits.[27] Furthermore, these findings suggested the importance of including disease-specific immune response measures to identify the modifications that may influence disease activity and outcomes. Another meta-analysis conducted in HIV/AIDs was similarly positive. Fifteen controlled trials were included in the analysis, which concluded that behavioural interventions in this population were effective in improving symptoms of stress, depression, anxiety, and anger. However, the connection to immunologic improvements, as measured by cluster of differentitation 4 cell counts, was more modest. Further research into the complex relationship between the immune system and behavioural health was recommended.[28]

Such results are not limited to disease-bearing populations. Caregivers of individuals with dementia who took part in a five-session structured support group experienced improvement in many psychosocial domains, including depression scores, anxiety, and anger. Statistically significant improvements in NK cell activity were also observed.[29] Though some relationships need further exploration, the link between psychosocial well-being and the immune system is generally robust.[30] These examples provide a basis for further exploration of the immune system as an outcome of interest in behavioural interventions. If positive outcomes are achieved, the implementation of such multimodal examinations will provide a biological basis for the benefits conferred by behavioural interventions. Moreover, with improved methodological rigor, such as including larger sample sizes, randomised controlled designs, and further exploration in diverse disease types, a causal relationship may be established between perceived psychosocial well-being and immune function.

RESEARCH METHODS FOR ASSESSING IMMUNE FUNCTION

Autoimmune diseases are one such subset of conditions where the underlying pathogenesis warrants a tailored approach to assessing changes in immune function. In the case of SLE and rheumatoid arthritis, disease pathogenesis is regulated largely by T cells. Downregulation of regulatory T cells and an increase in the number of effector T cells leads to the characteristic symptoms of inflammation, tissue damage, and autoantibody production.[31,32] T cells may be the most relevant immunologic outcome measure for behavioural interventions in autoimmune disease as it plays the greatest role in modifying disease characteristics. One study has explored this in SLE and found positive relationships between decreases in patient-reported depression and anxiety and T helper Type 1/T helper Type 2 cytokine balance following a 12-week behavioural intervention.[33] Future investigations may benefit

from exploiting these same methods in a larger sample size with a randomised controlled design to indicate causality.

CONCLUSION

Immune function is closely linked with other aspects of human health, whether directly through an immune response to a pathogen, or indirectly in the cases of cortisol/allostatic load and autoimmune disease. However, these relationships have been understudied in the domain of behavioural interventions. Behavioural intervention is a broad term with many applications towards different diseases and conditions, but most notable for negative psychological states. With the potential positive impact behavioural interventions can bring upon this domain of health, it is of paramount importance that appropriate measures of intervention success are employed. For this reason, as well as the connection between the immune system and psychological health, there is an imperative for measures of immune function to be increasingly implemented in gauging the success or failure of these programmes. Aside from the previously outlined associations and ability to detect meaningful physiological changes, these measures may provide additional benefits to researchers.

First, as previously discussed, there are several types of measures that can be employed for various study designs or variables of interest, giving this form of data a wide range of applications. Second, previous studies indicate that they are reliable and able to provide consistent measurements, which can be correlated with other data, used as a controlling variable, or used as primary/secondary outcome variable.[34,35] Where they are not as reliable, they are convenient; for example, with salivary cortisol. Collecting and analysing samples is simple (mouth swab) and does not require extensive lab equipment. However, this method is subject to notable variation depending on the time samples are collected and whether the subject has recently consumed a beverage.[35]

Nevertheless, other measures of immune function can be made easier to analyse through collaboration for a holistic approach to disease modification. There is evidence to suggest that frozen blood samples can be assessed for cytokines and other markers of immune activity with similar variation as compared to fresh samples.[33] If gathering this type of data is not feasible for a localised research team, collaboration with a facility or research partner with the ability is a plausible option. Finally, many behavioural interventions include patient-reported outcomes as a primary variable of interest. In the context of trying to change an individual's behaviour, gathering patient perception and attitude is central to the success therein. However, there is noteworthy bias inherent to this model. A subject who has undergone an intensive behaviour modifying intervention is likely to report reduced stress due to the placebo effect as well as personal bias from having been a participant. For this reason, introducing an immunologic indicator of emotional well-being would help to remove this bias by showing the physiological effects of the intervention in concert with the patient-reported outcomes.

Overall, the association between immunologic function and various factors that behavioural interventions can influence is robust but not entirely complete. Therefore, it is important that researchers include these measures as an integral part of rheumatic research initiatives to close gaps in knowledge and show the biologic basis for interventions seeking to modify autoimmune disease pathogenesis through behaviour change.

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Paediatric Scleroderma: Kids Are Not Just Little Adults

Editor's Pick

My choice for the Editor's Pick in this issue is the article by Li and McCormick. The authors reviewed the clinical presentation patterns and morbidities associated with paediatric-onset juvenile localised scleroderma and juvenile systemic sclerosis, highlighting key differences in disease patterns, which may influence targeted therapy approaches.

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Abstract

The sclerodermas are autoimmune rheumatic diseases associated with pathological fibrosis of tissues. The two forms, localised scleroderma (LS [also referred to as morphoea]) and systemic sclerosis (SSC), have different patterns of organ involvement depending upon age of onset. Juvenile LS (JLS) has a poorer prognosis than adult-onset LS (ALS), while juvenile systemic sclerosis (JSSC) has a better prognosis than adult-onset SSC (ASSC).

Optimal care requires appreciating the major differences between paediatric- and adult-onset disease, as they affect treatment and management strategies. Because the majority of patients with JLS have deeper tissue involvement, systemic immunomodulator rather than topical treatment is needed to mitigate their risk for serious morbidity and functional impairment. JSSC initially has a lower frequency of vital organ involvement than ASSC, but organ involvement can progressively accrue over time, so prolonged, aggressive treatment regimens may be needed. The authors recommend the care team for patients with JLS and JSSC include a rheumatologist who will be experienced in assessing and monitoring the most common extracutaneous involvement (musculoskeletal), as well as other organ

involvement. Long-term monitoring of these patients into adulthood is essential; JSSC is a lifetime disease, while JLS can relapse or smoulder, with the disease activity focused in the deeper tissues.

The purpose of this review is to provide a clinically focused overview of JLS and JSSC disease patterns, highlighting differences between paediatric and adult-onset disease. The authors will review current care recommendations for JLS and JSSC, and discuss some of the challenges for their care, and areas for future research.

Key Points

1. Patterns of organ involvement for the two forms of scleroderma (localised and systemic) vary depending on age of onset. Juvenile localised scleroderma (JLS) has a poorer prognosis than adult-onset LS, while juvenile systemic sclerosis (JSSC) has a better prognosis than adult-onset SSC; JSSC is a lifetime disease, while JLS can relapse or smoulder.

2. Paediatric- versus adult-onset disease therefore impacts treatment and management strategies, with a detailed understanding of the patterns of these diseases needed to direct optimal care.

3. Screening frequency for organ involvement, duration of treatment regimens, and long-term monitoring should consider paediatric onset for JLS and JSSC, rather than mirroring adult strategies.

INTRODUCTION

The sclerodermas are a family of autoimmune rheumatic diseases characterised by activation of the adaptive and innate immune system, genetic and vascular involvement, and dysregulated fibrosis.[1,2] Both localised scleroderma (LS) and systemic sclerosis (SSC) are rare, with incidence of LS in the USA estimated to be 2.7 out of 100,000 persons,[3] and the incidence of SSC worldwide estimated to be 1.4 out of 100,000 person–years.[4] About one-quarter to one-third of all LS cases occur in children,[3] whereas paediatric cases account for <5% of all SSC cases.[5] As with most rheumatic diseases, there is a female predominance, but this is less pronounced for paediatric compared with adult-onset scleroderma (Tables 1 and 2).

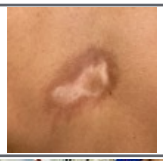
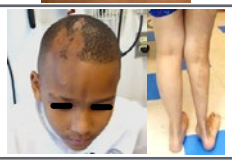
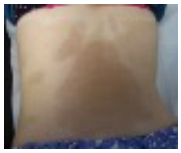
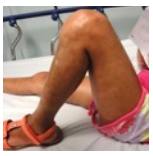
LS and SSC have distinct skin and organ involvement patterns with consequently different morbidity and mortality risks. Both diseases also have unique clinical patterns depending upon paediatric versus adult-onset. This review is focused on providing an overview of the current understanding of presentation patterns and morbidities associated with paediatric-onset LS and SSC.

The authors' review will compare the features of both groups, highlighting key differences in disease patterns, which are important to consider when deciding upon treatment and management. Paediatric rheumatologists treat most juvenile-onset patients with LS (JLS) with systemic immunomodulators to ensure adequate suppression of inflammation, and reduce the risk for damage development. This strategy has greatly improved outcome for JLS over the past decade, with a reduction in the frequency of arthropathy, limb length differences, and need for surgical intervention. On the other hand, understanding of how best to treat juvenile-onset SSC (JSSC) remains limited, due to the great rarity of this disease. The authors discuss some of the challenges for JLS and JSSC care, and areas for future research.

LOCALISED SCLERODERMA: CLINICAL FEATURES

LS, also known as morphoea, is recognised to have several subtypes that differ in skin lesion shape (ovoid, linear, or circumferential), lesion size, and disease extent (small or very limited to widespread). These subtypes are associated

Table 1: Differences in subtype and extracutaneous patterns between paediatric- and adult-onset localised scleroderma.[1-7]

	Paediatric	Adult	p
Onset age (years)	8.7	47	<0.001
Female:male	2.7:1	3.4:1	0.003
Disease duration (years; mean [range])	13.5 [2–40]	5.8 [1–28]	
Subtype pattern (%)			
Circumscribed morphoea 	21.6	61.4	<0.001
Linear scleroderma 	56.4	9.7	<0.001
Generalised morphoea 	7.3	21.7	<0.001
Pansclerotic or deep morphoea 	1.1	4.1	<0.001
Mixed morphoea	13.6	2.6	<0.001
Linear scleroderma subtype (%)			
Extracutaneous frequency	46.7	18.8	<0.001
Linear of head: neurological symptoms	45.1	23	<0.001
Linear of head: ECDS	60.6	73.3	0.019
Linear of head: PRS	19.1	16.4	NS
Linear of head: ECDS+PRS 	20.2	9.5	0.005

Subtype designation based upon the Padua preliminary classification criteria.[6] Pansclerotic morphoea and deep morphoea were grouped together because several of the sources used for generating this table used a different classification criteria than the Padua Criteria.

ECDS: en coup de sabre; PRS: Parry–Romberg syndrome; NS: not specified.

Table 2: Differences in subtype and organ involvement patterns between juvenile and adult-onset systemic sclerosis.

	JSSC	ASSC	p
Patient number	830	21,601	
Age (years; mean)	11.0	54.7	NS
Age onset (mean)	9	47	NS
Female/male ratio	3.8	5.3	<0.001
	% (number of patients)		
Subtype			
Diffuse	69.9 (357)	32.1 (6,931)	<0.001
Limited	20.8 (98)	56.9 (9,750)	<0.001
Overlap	23.1 (102)	11.7 (1,051)	<0.001
Sclerodactyly	66.9 (289)	72.1 (936)	NS
Vascular	89.9 (179)	97.9 (3,081)	<0.001
Raynaud's phenomenon	85.2 (534)	95.8 (9,451)	<0.001
Musculoskeletal	61.5 (236)	39.1 (1,267)	<0.001
Arthritis	32.5 (148)	16.9 (2,209)	<0.001
Tendon friction rubs	9.5 (31)	9.4 (1,024)	NS
Heart	11.7 (52)	16.2 (1,406)	0.009
Lung: interstitial lung disease	30.0 (152)	39.1 (6,083)	<0.001
Gastrointestinal	43.7 (176)	65.6 (3,754)	<0.001
Kidney: renal crisis	1.2 (3)	3.7 (248)	0.044
Serology			
Antinuclear antibody	84.4 (658)	90.5 (14,966)	<0.001
Anti-topoisomerase I (Scl 70)	29.1 (191)	26.9 (5,375)	NS
Anti-centromere	8.1 (37)	28.7 (6,101)	<0.001
Anti-PM/Scl	15.3 (30)	4.6 (125)	<0.001

Data in the table was compiled from 19 JSSC studies[5,8-25] and 10 adult SSC studies.[26-35] The percentage affected was determined based upon cohort size for a given feature, with parenthesis indicating the reported number of patients affected. Studies differed in their terminology, so the authors scored the following as representing interstitial lung disease: pulmonary fibrosis, abnormal forced vital capacity, abnormal HRCT. P-values were calculated using the Z-score test for two population proportions (significant at $p<0.05$).

ASSC: adult-onset systemic sclerosis HRCT: high resolution CT; JSSC: juvenile systemic sclerosis; NS: not specified.

with differences in functional impact risks (nil to high). Most adults with LS have circumscribed morphoea, which is also known as plaque morphoea, and is the mildest subtype (Table 1). Plaque morphoea lesions are superficial, affect only the skin, and typically very limited in extent. The next most common adult LS subtype is generalised morphoea, consisting of larger plaque lesions that occur on at least two anatomic regions (head, anterior torso, posterior torso, right and left upper and lower extremities).[36] Generalised morphoea lesions are usually also superficial in depth.[6]

The pattern is very different for paediatric-onset disease. Most patients with JLS have linear scleroderma, so-called because the lesions have a band-like appearance (Table 1).[36] Linear scleroderma lesions usually affect deeper tissues such as muscle and bone. They can extend across the entire length of a limb, onto the torso, or across the face and scalp following an embryonic pattern known as Blaschko's lines.[37] Pansclerotic morphoea is the rarest and most severe LS subtype. Skin involvement is circumferential and confluent on the limbs, with extension often onto the torso and sometimes the head.[36] Lesions often affect underlying tissues, predisposing the patient to chronic skin ulceration, with attendant risks of sepsis and squamous cell carcinoma.[38] This subtype has been reported to be more common in JLS than adult-onset LS (ALS).[36,38] Another subtype more common in JLS than ALS is mixed morphoea, which refers to a combination any of the other four subtypes (circumscribed, linear, generalised, or pansclerotic [Table 1]). Most commonly, mixed morphoea presents as linear scleroderma with one of the other subtypes.[1] Age-associated differences are also found within the linear scleroderma subtype, specifically for craniofacial linear scleroderma. Craniofacial linear scleroderma can present as a typical band-like lesion (en coup de sabre [ECDS]) or as progressive hemifacial atrophy. Progressive hemifacial atrophy, also known as Parry–Romberg Syndrome (PRS), affects deeper tissues without visible inflammation in the overlying skin.[36] Compared to ALS, JLS has a lower frequency of ECDS but a higher frequency of the combination of ECDS and PRS (Table 1).

For most patients, severe morbidity is related to extracutaneous involvement, which is associated with functional impairment and higher physician damage scores.[39,40] Extracutaneous involvement typically localises near the site of skin involvement, but presents remotely in 25–30% of patients.[41] Onset of extracutaneous manifestations usually follow skin disease onset, with neurological involvement reported a mean of 4.3 years after.[42] Late delays of 1–2 decades has also been reported,[43,44] and about 16% of neurological problems precede skin disease.[42]

Functional impairment has been reported in 27–38% of patients with JLS. Most commonly, this manifests as musculoskeletal.[39,45] Most patients with linear scleroderma of the limb or trunk have musculoskeletal impairment, from inflammatory (arthritis, myositis, fasciitis, tendonitis) and/or fibrosis related (joint contractures, angulation defects, muscle atrophy, limb length differences) problems.[40,46] Patients with linear scleroderma of the head are especially at risk for neurologic, ocular, and oral morbidities, including seizures, peripheral neuropathy, uveitis, enophthalmos, and dental root defects.[41,42,47]

Extracutaneous manifestations are more commonly reported in JLS than ALS.[47,48] In a retrospective study of patients with adult and paediatric LS, patients with JLS had a 32.5% frequency of musculoskeletal, ocular, oral, and neurologic morbidities compared with 8.0% in adults.[7] Prospective studies have identified still higher frequencies of extracutaneous manifestations (46–74%) in JLS.[40] This higher frequency in JLS than ALS partly reflects subtype differences, as linear scleroderma has a higher prevalence of deep tissue involvement than circumscribed or generalised morphoea (64% versus 32–46%, respectively).[6]

Age-associated differences in extracutaneous manifestations within the linear scleroderma subtype have also been identified. There was over a two-fold greater frequency of extracutaneous manifestations in paediatric compared to adult-onset linear scleroderma (47% versus 19%, respectively; $p<0.001$).[1] Neurological involvement was also about twice as prevalent in patients with JLS versus patients with ALS craniofacial linear scleroderma, with higher frequencies identified for seizure, headache, and neuroimaging abnormalities.[1] Many other severe neurological problems,

including movement disorders, Rasmussen's encephalitis, hemiplegic migraines, and cognitive and behavioural issues have been reported in JLS, but either very rarely or not at all, in ALS.[42,48]

The greater severity and higher frequency of extracutaneous manifestations in JLS compared with ALS is likely related to the disease spanning childhood, putting the child at risk for disturbed growth in affected areas during development. A two-fold higher frequency of extracutaneous manifestations in JLS was found for disease onset <10 years versus >10 years.[49] Children with JLS can develop haemiatrophy of the affected body region (face, trunk, limb), joint contractures, and angulation defects. Furthermore, aberrant positioning of structures on affected sites such as the eye and teeth can lead to vision loss and malocclusion. Growth disturbances were identified in 39% of patients with JLS in a review of retrospective studies, and in 26% and 46% of patients, respectively, in two different prospective studies.[40,50,51]

JUVENILE LOCALISED SCLERODERMA TREATMENT

Paediatric rheumatologists are in consensus on systemic immunomodulator treatment for patients with active disease at risk for major morbidities.[52,53] A recent Cochrane review supports methotrexate treatment for JLS, and this is also endorsed by the European Dermatology and Japanese Dermatology Associations.[54-56] There has been one double blind, placebo controlled, randomised clinical trial of methotrexate treatment conducted in JLS, along with numerous case series and open label studies.[51,57-59] Overall, the change from topical to systemic methotrexate treatment has been associated with major improvements in outcome. A comparison of patients with JLS pre-methotrexate to current cohorts showed a marked reduction in the frequency of joint involvement (50% to 20–23%, respectively), severely impaired function (22 to 11%, respectively), and orthopaedic surgical intervention (41% to 14%, respectively).[50]

Table 3: Recommendations for treatment of patients with juvenile localised scleroderma at risk for significant morbidity.

The treatments listed are recommended for patients with active disease who are at risk for significant morbidity from uncontrolled disease.

Active skin disease features include:
- Visible features: erythema, violaceous colour, waxy white or yellow colour, or worsening hair loss on head (based on serial photographs)
- Disease extension: new, larger, or deeper lesion based upon serial photographs or imaging studies. The new or larger region should have an active skin feature, not just a damage sign such as hyperpigmentation
- Tactile features: skin thickening alone or as part of waxy lesion, and tactile lesion warmth

Active extracutaneous disease features include:
- Arthritis, myositis, tendonitis, fasciitis, or uveitis
- Potential other extracutaneous activity features include new onset or worsening of headaches, seizures, arthralgia, neuropathy, or growth differences

Disease features associated with a risk for significant morbidity include either of the following:
1. A subtype associated with deep tissue and/or extensive skin involvement. These include circumscribed deep morphoea, linear scleroderma, generalised morphoea, pansclerotic morphea, and mixed morphoea
2. Extracutaneous morbidity (e.g., arthropathy, muscle atrophy, facial hemiatrophy, seizure)

Table 3 continued.

Recommended systemic immunomodulator regimens for juvenile localised scleroderma.				
	CARRA[60]		SHARE[52]	
	Dose	Dosing frequency, regimen	Dose	Dosing frequency
Methotrexate	1 mg/kg (maximum 25 mg) Subcutaneous route preferred	Weekly	15 mg/m^2 (maximum 25 mg)	Weekly
Corticosteroids: oral prednisone or prednisolone	• 2 mg/kg (maximum 60 mg) • 1 mg/kg (maximum 30 mg) • 0.5 mg/kg (maximum 15 mg) • 0.25 mg/kg/d (maximum 7.5 mg)	Divided to give twice daily for 2–4 weeks, then taper to 1.00 mg/kg daily by 8 weeks; to 0.50 mg/kg daily by 16 weeks; to 0.25 mg/kg daily by 24 weeks; off by 48 weeks	1–2 mg/kg	Daily for 2–3 months, then taper
Corticosteroids: intravenous pulse methylprednisolone	30 mg/kg (maximum 1,000 mg)	3 consecutive days/month for 3 months, or 1/week for 12 weeks	30 mg/kg	Not specified
Mycophenolate mofetil	• 600 mg/m^2/dose if <1.25 m^2 • 750 mg/dose if 1.25-1.5 m^2 or 40-50 kg • 1000 mg/dose if >1.5 m^2 or >50 kg	Twice daily		

Patients with JLS are more likely to develop major morbidity than those with adult onset LS due to the higher frequency of extracutaneous involvement and subtype pattern differences. Paediatric rheumatology organisations are in consensus to treat JLS patients with active disease at risk for significant morbidity with systemic immunomodulators. Criteria for active disease and patient characteristics associated with risk for significant morbidity were generated by the LS workgroup of CARRA for use in potential comparative effectiveness studies.[60] These criteria were not intended to qualify or disqualify patients for any specific treatment.

Both CARRA and SHARE generated methotrexate-based treatment regimens for these JLS patients. CARRA generated three methotrexate dose regimens (consensus treatment plans [CTP]) that differ based upon inclusion and type of corticosteroid: methotrexate alone, methotrexate with oral corticosteroids, or methotrexate with intravenous corticosteroids.[60] The three CTPs reflect best available evidence and current treatment practices of the CARRA membership. Current data is insufficient to support one CTP as superior, so CTP choice is the decision of the treating physician and family. SHARE has specified that methotrexate could be used with initial corticosteroid treatment, with general suggestions provided for corticosteroid dosing.[52]

For patients intolerant of or non-responsive to methotrexate, CARRA also generated a mycophenolate mofetil regimen that can similarly be used alone, or in conjunction with corticosteroids.[60] Co-administration with methotrexate can also be done.

CARRA: Childhood Arthritis and Rheumatology Research Alliance; CTP: consensus treatment plans; JLS: juvenile localised scleroderma; LS: localised scleroderma; SHARE: Single Hub and Access Point for Paediatric Rheumatology in Europe.

Two paediatric rheumatology groups (Single Hub and Access Point for Paediatric Rheumatology in Europe [SHARE], and Childhood Arthritis and Rheumatology Research Alliance [CARRA]) generated standardised methotrexate regimens which are shown in Table 3.[52,60] Three CARRA regimens were generated, which differ based upon corticosteroid inclusion and type; data was insufficient to support consensus on a single regimen. CARRA also generated criteria to define patients appropriate to treat with these regimens in treatment studies and tools to evaluate response, including for scoring skin activity and extracutaneous morbidity.[51,52,61] Ideally, these regimens will be used in comparative effectiveness studies to identify the most

effective regimen, and continue in an iterative fashion to identify the 'best' regimen.[60] A pilot study, although underpowered for determining the relative effectiveness of the regimens, showed the feasibility of this approach, with all three regimens found effective.[51]

Methotrexate treatment, with or without corticosteroids, is effective for almost 70% of patients.[51,57] Factors associated with poorer response to methotrexate treatment include presence of extracutaneous manifestations, some subtypes (linear scleroderma, mixed morphoea, pansclerotic morphoea), and treatment delay.[40,51,59,62] For patients who are non-responders, or intolerant to methotrexate, mycophenolic mofetil is most commonly substituted. Dosing regimens for mycophenolic mofetil were also generated by CARRA (Table 3.)[60] Small case series have reported benefit for biologic agents such as abatacept and tocilizumab for JLS (reviewed in Vasquez-Canizares N et al.;[1] a more detailed discussion of treatment management, including an algorithm, can be found here).

Duration of treatment is commonly 2 or 3 years, but relapses still occur in 22–44% of patients.[62-64] Re-treatment is effective at controlling relapse, but some patients will have persistently active, chronic remitting/relapsing, or evolving disease for decades.[45,65] Despite improvements in treatment strategies, >25% patients with JLS still have functional impairment, bone size difference, and/or joint limitation.[40,51]

SYSTEMIC SCLEROSIS: CLINICAL FEATURES

There are several differences between JSSC and adult-onset SSC (ASSC), including gender (lower female predominance in JSSC), subtype predominance, organ involvement, and autoantibody profile. Table 2 presents data compiled from 19 JSSC studies,[5,8-25] and 10 adult SSC studies.[26-35] The JSSC studies were selected based upon a limited literature review, and include the largest recent cohorts that described subtype and organ involvement. Several older international cohorts that reported on a minimum of three patients with JSSC were included. The adult studies were selected based upon their inclusion of large number of patients where the frequency of most organ systems was described, selecting cohorts representing different international populations.

Limited cutaneous is the most common ASSC subtype, followed by diffuse cutaneous. In contrast, diffuse cutaneous is the most common paediatric subtype, followed by overlap (Table 2). As expected from the lower frequency of limited cutaneous subtype, there is a much lower frequency of anti-centromere antibody in JSSC than ASSC. No age-related difference was found for the frequency of anti-Scl70 positivity (Table 2). A higher frequency of anti-PM/Scl antibody positivity was identified in JSSC, which likely partly reflects the greater frequency of the overlap subtype.

The frequency of sclerodactyly is similar across ages, while other musculoskeletal involvement is more common in JSSC (Table 2). Patients with JSSC have a lower frequency of vital organ involvement than ASSC, resulting in a lower mortality rate (10 years mortality rate: 15% for JSSC, 34% for ASSC in 2002).[14,66] The most common mortality patterns in JSSC is rapid disease progression that results in death within 5 years of diagnosis.[67]

Gastrointestinal involvement in JSSC is common, with low BMI and weight loss frequently reported.[10,16-19] Compared with other paediatric rheumatology diseases, JSSC was associated with the lowest body mass index Z scores, with 28% of patients with JSSC having a Z score of -1 or lower.[19] As with adults, oesophageal involvement can be asymptomatic, or associated with dysphagia, gastroesophageal reflux disease, and retrosternal pain.[68] Also, similar to ASSC studies, oesophageal involvement in JSSC is associated with lung involvement, such as lower forced vital capacity, and pulmonary symptoms (dyspnoea, cough).[68]

JUVENILE SYSTEMIC SCLEROSIS TREATMENT

Consensus recommendations for JSSC care were recently published by a SHARE group.[69] The rarity of JSSC has made treatment studies difficult, so recommendations are generally based upon descriptive case-control studies, or expert opinion.[69] Lung evaluation using high resolution

computerised tomography and pulmonary function test with diffusing capacity for carbon monoxide is recommended, and routine pulmonary function test monitoring is also recommended at least every 6 months. Cardiac (echocardiogram), skin, and renal monitoring should be monitored at a similar frequency. For JSSC, there is a need for reliable and validated outcome measures. An international effort is currently underway to develop consensus outcome measures based upon a systematic literature review, surveys, and Delphi process. This effort should help to standardise care, and enable international comparative studies.[70]

The SHARE panel recommends that treatment with systemic immunomodulatory drug(s) be considered for all patients with JSSC at diagnosis.[69] They recommend systemic corticosteroid treatment be considered in addition to a disease modifying anti-rheumatic drug. The high frequency of arthritis and rarity of renal crisis in patients with JSSC (Table 2) supports the use of systemic immunomodulators, including corticosteroids, for these patients. The rise in prevalence of pulmonary fibrosis in patients with JSSC over time, rising to 63% in diffuse cutaneous and 14% in limited cutaneous at 20 years, also supports this treatment strategy.[71] Case studies of refractory patients with JSSC have reported impressive benefits for lung and heart disease from tocilizumab or rituximab treatment.[72,73] The tocilizumab treated patients previously failed cyclophosphamide and mycophenolate mofetil treatment, and were still able to respond well to tocilizumab a mean of 6.9 years later.[72] Nintedanib, an anti-fibrotic agent found effective for slowing lung progression in adult patients with SSC, was recently approved for treatment of adult SSC interstitial lung disease.[74] It is currently being studied in a double blind, placebo controlled, randomised clinical trial in paediatric patients with interstitial lung disease,[75] and may be available for treating patients with JSSC in the near future.

CONCLUSIONS

Paediatric-onset localised scleroderma and systemic sclerosis both differ from adult-onset disease in several major clinical features. These major differences imply the need for paediatric scleroderma specific care and treatment strategies, rather than relying solely upon adult strategies. It is important for adult providers to appreciate these differences so they can provide the appropriate care and monitoring for these patients when they transition to adult care. Because musculoskeletal involvement is present in the majority of patients with JLS and JSSC, the authors recommend that care teams for these patients include a rheumatologist, who will be able to identify the development and progression of musculoskeletal and other extracutaneous involvement. Other subspecialists are also often needed for care, especially for patients with paediatric-onset SSC.

JLS is more severe than adult-onset LS, with a higher prevalence of extracutaneous involvement and longer active disease duration that spans childhood. These features put patients with JLS at risk for functional impairment and disfigurement from a wide range of morbidities, such as limb length differences, arthropathy, seizures, and facial hemiatrophy. Treatment to control active disease with methotrexate and other systemic immunomodulators is currently the best strategy to limit the risk for, and level of damage, and has greatly improved outcomes. Relapses are common, and may even present remotely as new or worsening extracutaneous morbidity, so long-term monitoring of these patients through adulthood is vital.

JSSC has a lower mortality rate than adult-onset SSC, but still ranks as one of the most severe paediatric diseases due to substantial morbidity from skin, musculoskeletal, gastrointestinal, and lung disease. JSSC may have a higher incidence of inflammation than adult-onset disease, with a higher frequency of overlap subtype and arthritis. Lung disease may also continue to progress over decades in JSSC patients, so long-term aggressive treatment may be warranted to minimise morbidity and mortality risks. Recent consensus care recommendations specify that all new patients should be considered for systemic immunomodulator and corticosteroid treatment.

Overall, more research is needed for both JLS and JSSC. Paediatric rheumatology organisations have generated several treatment regimens and measures for JLS to assess response. More JLS treatment studies, including comparative effectiveness studies, are needed to identify the most effective regimens, especially for patients

that continue to have functional impairment, growth disturbances, neurological symptoms, or who are methotrexate non-responders, or are methotrexate intolerant. Research in JSSC has lagged behind JLS due to the greater rarity of JSSC, and the lack of consensus outcome measures. A current international effort to generate consensus measures that can be used in international JSSC treatment studies should advance care by enabling more data-based recommendations. The enormous, continued advances in adult SSC knowledge of disease pathophysiology and treatment also offer great hope and promise to improve the outcome for patients with paediatric-onset disease.

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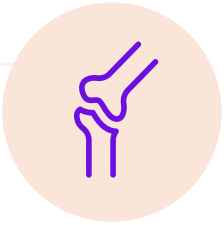
Type I Interferons in the Pathogenesis and Treatment of Sjögren's Syndrome: An Update



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Abstract

Type I interferons (IFN) are widely expressed cytokines that play a pivotal role in the cell-intrinsic antimicrobial process, especially in viral infections. Studies have shown an increased expression of Type I IFNs and their induced genes in peripheral blood cells and exocrine glands from patients with Sjögren's syndrome (SS), indicating that the Type I IFN pathway a vital role in the pathogenesis of this disease.

The source of upregulated Type I IFNs in patients with SS is unknown. Many cells were reported to contribute to the process, especially plasmacytoid dendritic cells and other innate immune cells.

The activation of Type I IFN signalling was regulated by both genetic and epigenetic pathways, suggesting that genetic predisposition and environmental factors may affect the initiation and progression of SS. Treatments targeting the Type I IFN pathway are still under evaluation and more results are needed to see their value.

The authors' review aims to summarise the functions and regulations of Type I IFNs in the pathogenesis of SS. They also summarise current treatments (including clinical trials) targeting the Type I IFN pathway in treating SS and provide potential targets for future studies.

Key Points

1. Type 1 interferons (IFN) and their induced genes have been found to have increased expression in Sjögren's syndrome (SS), with increased expression correlating with clinical features in SS.

2. Activation of signalling for Type 1 IFNs and their induced genes is regulated by both genetic and epigenetic pathways; this suggests that genetic predisposition and environmental factors affecting IFN may alter onset and progression of SS.

3. Treatments that target blocking of Type 1 IFNs could provide a promising avenue for treatment of SS; results of ongoing clinical trials for SS and other auto-immune diseases are eagerly awaited.

INTRODUCTION

Interferons (IFN) are a class of cytokines that are produced in response to pathogenic stimuli.[1] The IFN family was divided into three classes: Type I, Type II, and Type III. Type I IFNs are widely expressed cytokines that play a pivotal role in the cell-intrinsic antimicrobial process, especially in the context of viral infections.[2] They mobilise innate immune responses by enhancing antigen presentation and cytotoxicity effect, while restraining the magnitude of inflammation to avoid toxicity.[2] They can also affect the adaptive immune system by promoting the functions of T and B cells in various ways.[2,3]

In humans, IFN-Is consist of 13 IFN-α subtypes, IFN-β, IFN-κ, IFN-ε, IFN-δ, and IFN-ω. IFN-α is produced by haematopoietic cells, in particular plasmacytoid dendritic cells (pDC), while IFN-β can be produced by most cell types. Although protective in acute viral infections, IFN-Is, especially IFN-α and IFN-β, have been implicated as deleterious in autoimmune diseases.[4,5]

Meanwhile, Type II IFNs, also known as IFN-γ, are released by cytotoxic T cells and T helper cells, playing a major role in building cellular immunity and priming the other two types of IFNs.[6]

Type III IFNs include four IFN-λ subtypes, which are mainly expressed by mucosal epithelial cells. They activate the same receptor-associated JAK and similar downstream pathways as IFN-Is by binding to different receptors;[7] thus, they may play a similar role as IFN-Is such as antiviral activity.[8] These two types of IFNs are beyond the scope of this review.

Sjögren's syndrome (SS) is a chronic autoimmune inflammatory disorder characterised by dryness of the eyes and mouth due to a functional impairment of the salivary and lacrimal glands. It has been found that lymphocytic infiltration and deposition of autoantibodies of exocrine glands cause chronic inflammation and functional impairment.[9] SS may also affect multiple organs, and not just exocrine glands, such as the skin, joints, lungs, gastrointestinal tract, kidney, vessel, and haematology and nervous systems.[10] Besides, chronic B cell stimulation in SS increases the risk of lymphoid malignancies,[11,12] SS can occur as a lone condition (primary SS) or accompanied by another connective tissue disease (secondary SS); both have similar presentations.[13] The pathogenesis of SS has yet to be fully elucidated.

In the past years, a number of studies have revealed the important role of IFNs in the initiation and progression of SS. Although the three types of IFNs have been implicated in the pathogenesis of SS, IFN-Is and their induced genes were correlated with clinical presentation, disease activity, and antibody titres of SS, enhancing our understanding of mechanisms of SS. This review focuses on the role of Type I IFNs, mainly IFN-α and IFN-β, and summarises their roles in the pathogenesis and treatment of SS.

TYPE I INTERFERONS SIGNALLING PATHWAY

Type I IFNs can be produced when stimuli like microbial products are sensed by various cellular receptors, which then induce IFN-stimulated gene (ISG) expression.[2] Production of Type I IFNs depends on the cell types and environment.[5] Innate immune cells such as macrophages and dendritic cells (DC) produce Type I IFNs after sensing stimuli by using varieties of pattern-recognition receptors (PRR), which function as sensors for pathogen-associated molecular

patterns. Toll-like receptors (TLR) are one of the important types of PRR. They are transmembrane proteins and detect pathogen-associated molecular patterns derived from extracellular bacteria or bacteria that have been taken into vesicular. Other pathogens sensing systems include retinoic acid inducible gene I (RIG-1), melanoma differentiation-associated protein 5 (MDA5, which is also known as IFIH1), stimulator of IFN genes protein, and nucleotide-binding oligomerisation domain-like receptors (NLR).

It is widely acknowledged that pDCs are the major producers of IFN-α (Figure 1). In pDCs, single strand RNA activates endosomal TLR7 or TLR8, which then activates IFN regulatory factor (IRF) 7 and/or IRF5. Double strand DNA activates endosomal TLR9, or RNAs activate cytosolic nucleic acid sensors MDA5 or RIG-1, all of which result in activation of IRF7. Translocation of IRF5 to the nucleus induces transcription of Type I IFNs and pro-inflammatory cytokines such as IL-6 and TNF. Translocation of IRF7 induces transcription of Type I IFNs, especially a high amount of IFN-α. Type I IFNs then bind to the Type I IFN receptor (IFNAR) in pDCs and activate the canonical JAK signal transducer and activator of transcription (STAT) pathway, resulting in transcription of ISGs. ISGs include IRF7, which provides a feed-forward mechanism for the production of more Type I IFNs.

In other innate immune cells such as phagocytes and DCs, stimulations come from both extra- or in-cell. Lipopolysaccharide binds to TLR4 on cytomembrane or double-stranded RNA, which activates endosomal TLR3 and will then activate IRF3 via TIR domain-containing adaptor molecule 1 (also known as TRIF), Lipopolysaccharide also activates nuclear factor-κB via myeloid differentiation primary response protein. RNAs activate MDA5 or RIG-I, or double strand DNA activate the DNA sensor cyclic GMP-AMP synthase and then the stimulator of interferon genes protein which all lead to the activation of IRF3. Translocation of IRF3 induces transcription of IFN-β. Translocation of nuclear factor-κB induces transcription of inflammatory cytokines.

As shown in Figure 2, IFN-α and IFN-β exert their immune functions by binding to cell surface receptor IFNAR, causing dimerisation of subunits IFNAR1 and IFNAR2, which activate tyrosine kinase 2 (TYK2) and JAK1 separately. Then, TYK2 and JAK1 phosphorylate STAT1 and STAT2 to form heterodimers, to which IRF9 bind and form the heterotrimeric complex IFN-stimulated gene factor 3. IFN-stimulated gene factor 3 translocates to the nucleus and initiates the transcription of ISGs by combining with IFN-stimulated response elements, producing antiviral and antitumour molecules and transcription factors such as IRFs.

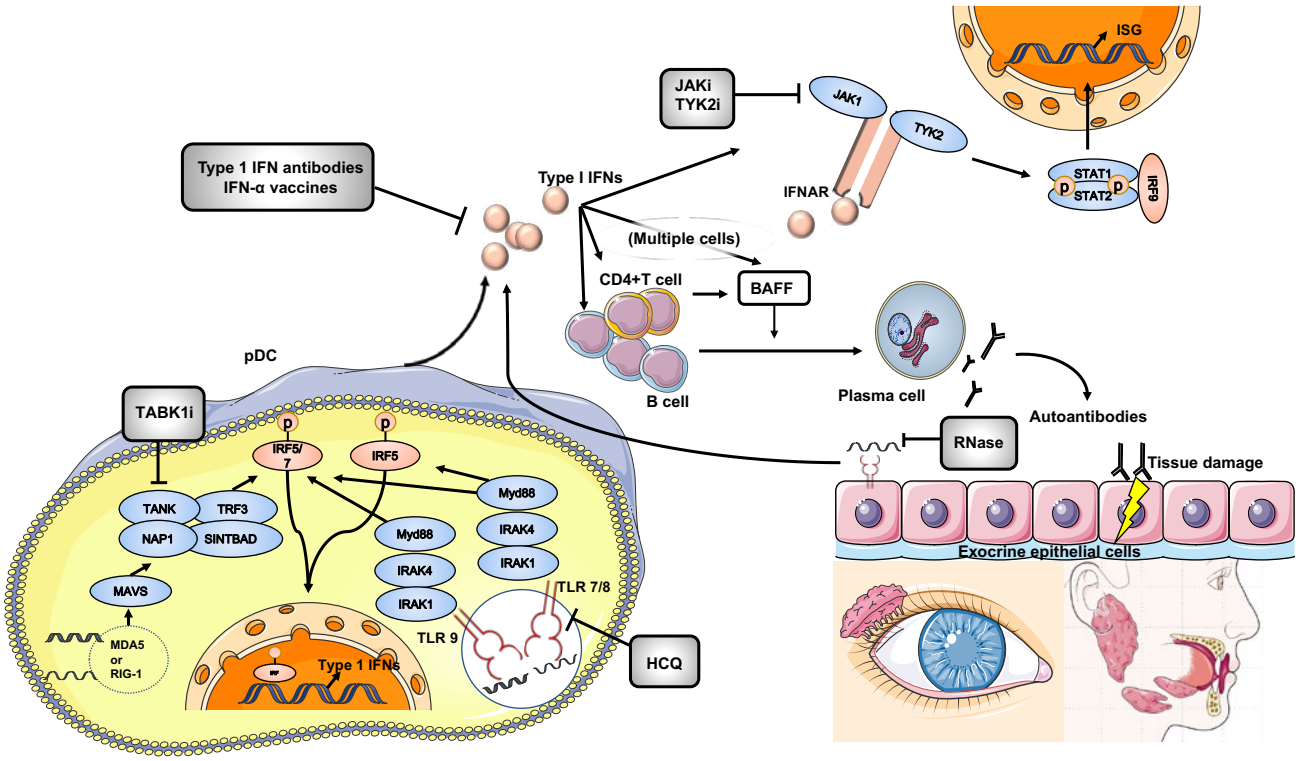
TYPE I INTERFERON SIGNALLING PATHWAY IN SJÖGREN'S SYNDROME

Studies have shown increased Type I IFNs in SS, correlating with clinical features. Researchers have found that IFN-α was over-expressed in minor salivary glands (MSG), ocular epithelial cells, plasma, and peripheral blood cells in patients with SS.[14-17] Nezos et al.[18] have found that Type I IFNs and Type II IFNs were overexpressed in peripheral blood and MSG from patients with SS compared with healthy control, while patients with SS and lymphoma had lower IFN-α and higher IFN-γ than patients with SS and without lymphoma. They further showed IFN-α/IFN-γ mRNA ratio in MSG was the best discrimination of lymphoma development in SS.[18]

Imgenberg-Kreuz et al.[19] demonstrated that IFN system activation correlated with adverse prognostic factors including younger age, more positivity of anti-SS-related antigen A (SSA) or SS-related antigen B antibodies, hypergammaglobulinemia, low C4, and lymphoma.[19] RNA-containing immune complexes can activate immune cells and produce Type I IFNs. Anti-SSA or SS-related antigen A autoantibodies were specific antibodies for SS that target RNA-binding proteins. They were found to induce Type I IFNs in peripheral blood mononuclear cells in people who are healthy, and correlated with activation of the IFN-I pathway in SS.[20]

Non-obese diabetic mice spontaneously develop autoimmune inflammation in the lacrimal and salivary glands and are considered a suitable model to study SS.[21] Chaly et al.[22] have found four upregulated genes related to male-specific lacrimal gland inflammation by gene expression analysis, three of which (*CXCL9*, *CCL19*, and *EPSTI1*) were dependent on Type I IFNs. Furthermore, they found IFNAR1-deficient mice were protected from

Figure 1: Major treatment targets of Type I interferon production in Sjögren's syndrome.



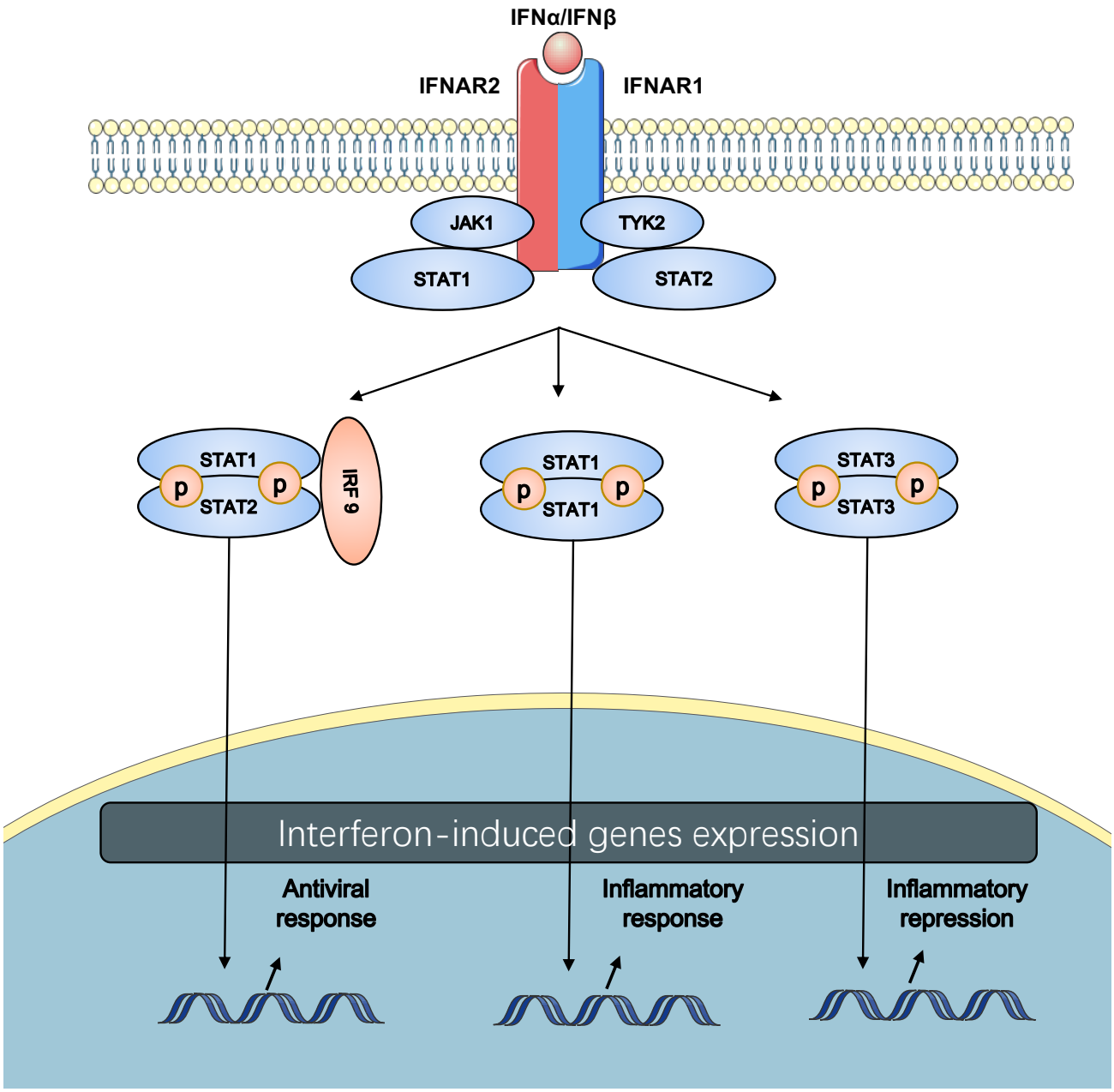
In Sjögren's syndrome, exocrine epithelial cells and infiltrating immune cells such as pDCs produce large amounts of Type I IFNs, inducing transcription of ISGs and pro-inflammatory cytokines through the JAK–STAT pathway. The overexpression of Type I IFNs induce B cell expansion and differentiation into plasma cells, which produce autoantibodies and cause organ damage. Type I IFN antibodies and IFN-α vaccines, which induce the production of IFN-α antibodies, inhibit the function of Type I IFNs. HCQ can prevent the activation of TLR7 and TLR9. TBK1i can prevent the activation IRF3 and IRF7. RNase digests circulating RNAs and inhibits Type 1 IFN production. JAKi and TYK2i are important in the downstream pathway of Type 1 IFNs and inhibit ISG expression.

BAFF B: cell activating factor; HCQ: hydroxychloroquine; IFNAR: Type I interferon receptor; IRAK: IL-1 receptor-associated kinase; IRF: interferon regulatory factor; ISG: interferon-stimulated genes; JAKi: JAK inhibitors; MAVS: mitochondrial antiviral signalling protein; MDA5: melanoma differentiation-associated protein 5; Myd88: myeloid differentiation factor 88; NAP1: nucleosome assembly protein 1; pDC: plasmacytoid dendritic cells; RIG-1: retinoic acid inducible gene 1; RNase: ribonuclease; SINTBAD: similar to NAP1 TBK1 adaptor; STAT: signal transducer and activator of transcription; TANK: TRAF family member associated NF-κB activator; TBK1i: TANK-binding kinase 1 inhibitor; TRF3: TATA-box-binding protein-related factor 3; TLR: toll-like receptor; TYK2: tyrosine kinase 2; TYK2i: tyrosine kinase 2 inhibitor.

dacryoadenitis. The results implicated that the Type I IFNs pathway is required for lacrimal gland inflammation in non-obese mice and suggested that the mechanisms of Type I IFNs in human SS.

The source of increased Type I IFNs in circulation and tissues was yet to be known, and many cells were reported to contribute to the process. Maria et al.[23] found an increased expression of IFN-I-induced genes in circulating immune cells, which was associated with increased disease activity in SS.[23] Considering pDCs are the major source of IFNs-I, Hillen et al.[24] performed RNA-sequencing of circulating pDCs from patients with or without SS and showed that SS pDCs produced higher levels of pro-inflammatory cytokines, including Type I IFNs, and Type I IFNs-induced gene signature, which was associated with disease activity. Besides, Lopes et al.[25] have performed an RNA-sequencing of monocytes from patients

Figure 2: The canonical Type I interferon signalling pathway.



Type I IFNs bind to IFNAR, which is composed of the IFNAR1 and IFNAR2 subunits, initiating a signalling cascade through JAK1 and TYK2. This activates STAT1 and STAT2. STATs get phosphorylated and dimerised and then translocate to the nucleus. Different STATs activate the different sets of genes involved in the biological process, including the antiviral and inflammatory response and inflammatory repression.

IRF9: interferon regulatory factor 9; STAT signal transducer and activator of transcription; TYK2: tyrosine kinase 2.

with SS and identified four molecular signatures in monocytes.[5] They were related to translation, IFN-signalling, and TLR signalling. Unsupervised hierarchical cluster analysis of the hub-genes identified one cluster characterised by a higher prevalence of anti-SSA antibodies, IFN score, and erythrocyte sedimentation rate, indicating that Type I IFNs altered transcriptional profile

of SS-monocytes and participated in the pathogenesis of SS. In another study by Blokland et al.,[26] patients with a high Type I IFN signature expressed elevated levels of Fas on innate lymphoid cells (Groups 2 and 3), supporting their role in the pathophysiology of SS.

Intrinsic factors may also contribute to Type I IFNs production. Long interspersed nuclear element 1 is one of the types of endogenous virus-like genomic repeat elements that are silent in normal conditions. It was reported that the expression of long interspersed nuclear element 1 was increased and correlated with the expression of IFN-I in the MSG from patients with SS.[27] This may also shed some light on the mechanisms of SS.

To express the activation of IFN-I signalling, the 'IFN-I signature' was proposed to describe the increased expression of a variety of IFN-1-regulated genes was observed in peripheral blood cells of patients with systemic lupus erythematosus (SLE).[28,29] Later, the IFN signature has also been found in other autoimmune diseases such as SS, myositis, rheumatoid arthritis, and systemic sclerosis.[30] Expression of Type I IFNs-induced genes in monocyte from patients with SS was correlated with B cell activating factor and disease activity.[31,32] Del Papa et al.[33] have found that patients with SS and systemic extra-glandular manifestations have higher Type I-regulated genes versus patients with a disease limited to glandular features. Recently, Cinoku et al.[34] have found that SS with lymphoma had higher expression levels of IFNs-I-induced genes, especially ISG15 in both labial MSG and peripheral blood, representing a novel biomarker for lymphoma development in SS. It should be noted that the IFN signature can be induced by either Type I IFNS or Type II IFNs, and it was difficult to differentiate them. Both types of IFNs participate in the pathogenesis and prognosis of SS.[18,35] More efforts are needed to develop more specific and sensitive methods to detect both signalling pathways and their distinct roles in SS.

Environmental factors such as viral infections were thought to trigger the development of SS in individuals with a susceptible genetic background.[36] Reports of familial aggregation, genome-wide association studies, and candidate gene association studies supported genetic and epigenetic factors of SS.[37] The major histocompatibility complex region was the strongest genetic predisposition to SS.[38-41] Other than major histocompatibility complex, the two largest genome-wide association studies also identified other polymorphisms that were associated with SS.[42,43] The strongest related genes, including *IRF5* and STAT4, play a role in the IFN gene signature. STAT4 is a transcription factor in the downstream of Type I IFNs signalling and initiates a transcription of ISGs. IRF5 acts downstream of Type I IFNs and forms a positive feedback loop to induce IFN-α production. However, the exact contribution of these genetic variations to the development of SS is still to be elucidated.

Epigenetic modifications are defined as changes in phenotype without alteration of DNA sequences, consisting of primarily DNA methylation, histone modifications, and non-coding RNAs. Epigenome-wide association studies have found Type I IFN-induced genes in MSG biopsies and, in different cell types, hypomethylation, which correlates with increased mRNA expression in patients with SS.[37]

MicroRNAs are small single-stranded RNA molecules that can bind to target messenger RNA and interfere with translation. Jang et al.[44] evaluated the expression of microRNAs in primary epithelial cells from SS salivary glands and found miR-1248 activated IFN-β through the direct interaction with RIG-I and argonaute 2. Functional studies established two aspects of miR-1248 that affect human salivary glands cells: one served as a ligand to RIG-I and induced IFN production, while the other suppressed the expression of messenger RNAs. Jara et al.[45] demonstrated that Type 1 IFNs could decrease the levels of hsa-miR-145-5p in salivary glands of patients with SS, leading to upregulation of Mucin 1 and TLR4, which contribute to salivary gland inflammation and dysfunction in patients with SS. In conclusion, both genetic and epigenetic factors could influence the activation of Type I IFN signalling in SS.

Post-translational modifications also play a role in regulating the Type I IFN signalling pathway.[46] Increased histone acetylation of IFN-inducible genes was correlated with their increased expression in autoimmune disease patients.[47] More information on the effect of post-

translational modifications to Type I IFN pathway need to be explored.

TREATMENT TARGETING THE TYPE I INTERFERON PATHWAY IN SJÖGREN'S SYNDROME

Although many clinical trials targeting the type I IFN pathway have been started, as summarised in Table 1 and Figure 1, few beneficial results have been published. A low dose of orally-administered IFN-α was found to exhibit anti-inflammatory activity through complex immune-mediated effects in patients with SS.[58] Successfully treating SS-associated neuropathy with IFN-α was reported in some cases, especially in patients with ganglionopathy.[59,60] However, IFN-α administered via the oromucosal route in a combined Phase II clinical trial increased salivary output but failed to meet coprimary endpoints in a combined Phase III study.[51,54] As a traditional treatment of SS, hydroxychloroquine is frequently used to treat SS by preventing the activation of TLR7 and TLR9, but failing to improve clinical response.[61]

Blocking Type 1 IFNs is a promising strategy for the treatment of SLE, and, therefore, could also be of interest in SS.[62] Anifrolumab, an anti-IFNAR monoclonal antibody, was approved by the U.S. Food and Drug Administration (FDA) on 2nd August 2021 and the European Medicines Agency (EMA) on 21st February 2022 as an add-on therapy for adults with moderate-to-severe SLE.[63] It is encouraging news for ongoing clinical trials targeting Type 1 IFNs in treating SLE.

IFN vaccination is successful in preventing SLE progression and improving survival by inducing neutralising anti-IFN-α antibodies in mouse models.[64] IFN-Kinoid, an IFN vaccine that can induce a disease-modifying polyclonal anti-IFN-α antibody with high IFN-α neutralisation capacities, was tested in a Phase IIb, randomised placebo-controlled study in adults with SLE with statistically down-regulated IFN signature, though the clinical coprimary endpoint (British Isles Lupus Assessment Group-based Composite Lupus Assessment [BICLA] response with corticosteroids tapering) was not met.[65,66] Nonetheless, secondary endpoints including SLE Responder Index (SRL) 4 with corticosteroids tapering and lupus low disease activity state showed superiority in the kinoid group.[65] Patients with active virus infection were excluded from the trial regarding an reduction of anti-viral effect of blocking IFN-α. However, no increased risk of viral infections was observed in kinoid group compared with placebo group. One limitation was that kinoid did not block IFN-ω, IFN-β, IFN-γ, or IFN-λ, which may also participate in the development of the disease. IFN kinoid was further used in treating mouse models with SS-like features, resulting in the reduction of Type I IFN signature and disease feature improvement.[67] However, there are no clinical trials on anti-IFN-α/IFNAR, and more clinical evidence is needed regarding the safety and efficacy of these drugs in SS.

Circulating RNAs can be sensed by PRR and induce Type I IFN production, RSLV-132, a human RNase fused to human IgG1 Fc domain. They have the ability to digest circulating RNAs and inhibit Type 1 IFN production. It was evaluated in a Phase II randomised double-blind placebo-controlled study with clinically meaningful improvements.[51] Larger randomised clinical trials are needed to further confirm its therapeutic effect.

TANK-binding kinase 1 is an important molecule downstream of RIG-I-like receptors, activating IRF3 and IRF7, which results in Type I IFN production. Recently, Bodewes et al.[68] demonstrated that TANK-binding kinase inhibition reduced the expression of ISGs in pDCs from patients who tested positive for Type I IFN, representing a potential treatment target in SS.

JAK inhibitors were in the important downstream pathway of Type I IFNs and have exhibited promising results in SLE. Baricitinib, a JAK1/2 inhibitor, has been tested in two double-blind multicentre randomised placebo-controlled Phase III trials for the treatment of SLE. In SLE-BRAVE-I trial (NCT03616912),[69] the baricitinib 4 mg oral dose met the primary endpoint for SRI4 response at Week 52 compared with placebo. However, the SLE-BRAVE-II study (NCT03616964),[70] which also studied adults with active lupus, neither met the primary endpoint of SRI4 response, nor key secondary endpoints. Considering the similar pathogenesis in SS, studies have been carried out on JAK inhibitors to treat SS. In mouse models, Lee et al.[71] demonstrated the filgotinib, a JAK1 selective

Table 1: Clinical trials of medicine targeting the Type I Interferon pathway in patients with Sjögren's syndrome.

Mechanism	Type of inhibitor	Medication	Type of study	Status	Results	Registration number or reference
IFN-α	Therapeutic vaccine: IFN-α	Low-dose human IFN-α	Combined Phase III	Completed	Increased UWS flow	Cummins MJ et al. (2003)[48]
IFN-α	Therapeutic vaccine: IFN-α	Low-dose human IFN-α	Phase II	Completed	Improved salivary output and decreased complaints of xerostomia	Ship JA et al. (1999)[49]
RNase	Human RNase fused to IgG1 Fc domain	RSLV-132	Phase II	Completed	Reduction of severe fatigue	NCT03247686;[50] Posada J et al. (2021)[51]
pDCs	Human monoclonal anti-ILT7 antibody to cause pDCs depletion	MEDI7734	Phase I	Completed	N/A	NCT02780674[52]
TLR	TLR inhibitor	Hydroxychloroquine	Phase III	Completed	No improvement of symptoms	NCT00632866;[53] Gottenberg J-E et al. (2014)[54]
JAK	JAK1, Syk, BTK inhibitor	Filgotinib, lanraplenib, tirabrutinib	Phase II	Completed	No significant superior effect	NCT03100942[55]
JAK	JAK1/JAK3 inhibitor	Tofacitinib	Phase II	Recruiting	N/A	NCT04496960[56]
JAKI	JAK1/JAK2 inhibitor	Baricitinib	Phase II	Recruiting	N/A	NCT05016297[57]

BTK: Bruton's tyrosine kinase; IFN: interferon; N/A: not available; pDCs: plasmacytoid dendritic cells; Syk: spleen tyrosine kinase; TLR: toll-like receptor; UWS: unstimulated whole saliva flow.

inhibitor, ameliorated the function of excretion and lymphocytic infiltration of the salivary gland. JAK1/3 inhibitor tofacitinib and JAK1/2 ruxolitinib also exhibited good responses *in vitro*.[72,73] Several interventional clinical trials are on-going and the results are not yet available (Table 1). A randomised Phase II double-blind, placebo-controlled study has assessed the safety and efficacy of JAK1 inhibitor filgotinib, TYK2 kinase inhibitor lanraplenib, and Bruton's tyrosine kinase inhibitor tirabrutinib in adults with active SS, separately (NCT03100942).[55] The primary study results reported on the clinical trials website showed that none of these three drugs were significantly superior to placebo. However, no conclusion can be reached until the full analysis is completed and official papers are published. The other Phase II trials involving tofacitinib and baricitinib were in the recruitment phase (NCT04496960 and NCT05016297).[56,57]

CONCLUSION

Type I IFN signalling plays a vital role in pathogenesis in SS and provides a promising intervention target for future studies. The sources of Type I IFNs and the induction of IFN signalling in SS still need to be fully elucidated.

There are several ongoing clinical trials, and their results are eagerly awaited. Thus, it is of great importance to further explore the role of Type I IFN signalling in SS and other autoimmune diseases.

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Ocular Manifestations of Loeys–Dietz Syndrome

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Abstract

Loeys–Dietz syndrome (LDS) is caused by connective tissue mutations; the resulting defective connective tissue in organs such as the eye may be related to ocular symptoms in patients with LDS. The aim of this study was to review different ocular manifestations in LDS. A literature review of articles published within the past 5 years was performed using Web of Science™ and PubMed to search for 'Loeys–Dietz' with the terms 'ocular' and 'ophthalmology.' Additional search terms were generated from the initial literature assessment, and 32 articles were ultimately reviewed. Reported ocular symptoms in LDS included hypertelorism, ocular misalignment, refractive errors, and more. For LDS, the most reported findings were hypertelorism (n=111), astigmatism (n=25), down slanting palpebral fissures (n=20), myopia (n=9), and strabismus (n=8). However, more research on ocular symptoms in LDS is needed.

Key Points

1. Studying the presence of ocular symptoms in Loeys–Dietz syndrome is important because of how it affects patient management.

2. The most referenced ocular findings for Loeys–Dietz syndrome included hypertelorism, astigmatism, and down slanting palpebral fissures.

3. A large database of the ocular involvement of these conditions could facilitate earlier detection and potential treatments.

INTRODUCTION

Loeys–Dietz syndrome (LDS) is a rare disorder of connective tissue, which classically presents with signs of hypertelorism, bifid uvula, aneurysms, or arterial tortuosity.[1] Previous categorisation of the LDS subtypes considered the phenotype to be strongly correlated with subtype; for example, craniofacial features were thought to be strongly associated with LDS Type I, and osteoarthritic features strongly associated with LDS Type III. There has since been a shift in thinking, such that each LDS subtype is now considered to be a combination of features.[2]

There are six types of LDS, caused by mutations in *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *TGFB3*, and *SMAD2*, respectively.[3] These genes are involved in the transforming growth factor-β pathway, which is critical for tissue development, differentiation, and maintenance.[4] Both *TGFBR1* and *TGFBR2* code for receptors in the pathway, which are acted on by cytokines coded by *TGFB2* and *TGFB3*, while *SMAD2* and *SMAD3* help to mediate the signals of this pathway.[3] Ocular embryogenesis begins with the development of the optic vesicles, which are influenced by several signalling molecules, including the transforming growth factor-β.[5] Thus, it follows that there might be ocular abnormalities in patients with LDS. This study sought to review the ocular manifestations of LDS, as well as their relative frequencies.

METHODS

A literature review was performed using Web of Science™ and PubMed. Eligibility criteria included whether the studies were published within the past 5 years and written in English, however, all types of articles were included due to the niche topic area. Initially, the terms 'Loeys–Dietz, 'ophthalmology', and 'Loeys–Dietz, 'ocular' were searched; more specific search terms were then generated from the articles generated in the initial search. Those additional terms used were: 'eye', 'retina', 'retinal detachment', 'xerophthalmia', 'lenticular', 'lens opacity', 'glaucoma', 'myopia', 'canthal', 'canthal rhytids', 'sclera', 'scleral fragility', 'ocular fragility', 'microcornea', 'angioid streaks', 'vitreous', 'brittle cornea', 'globe perforation', 'keratoconus', 'keratoglobus', 'refractive error', 'cornea', 'corneal fragility', 'corneal rupture', 'corneal hydrops', 'lens subluxation', 'conjunctivochalasis', 'Bruch's membrane', 'choroidal neovascularisation', 'exotropia', 'central corneal thickness', 'ectopia lentis', 'cataract', 'hypertelorism', 'craniofacial', and 'astigmatism'.

The titles, abstracts, and full texts were reviewed for each potential article. The internal validity of each study was rated by two reviewers. An initial evaluation of internal validity was assessed using the National Institutes of Health (NIH) Study Quality Assessment Tool. However, due to the large number of case reports in this study and the inability to find a broadly appropriate category to assess these reports, the Joanna Briggs Institute (JBI) method was ultimately used.

RESULTS

Loeys–Dietz Syndrome

After the exclusion criteria were applied, there were 32 appropriate articles, which described a total of 275 patients (Table 1).

Craniofacial

Hypertelorism is commonly reported in patients with LDS.[6-28] It was documented in 111 out of 275 patients in the articles that the authors reviewed. However, one study assessing ocular complications in patients with LDS versus controls found that interpupillary distances were similar in the eyes of the patients with LDS and the control patients. This is interesting because hypertelorism is considered to be a common clinical finding associated with LDS. However, no specific measurements were noted in the original report describing this phenotype.[29]

Down slanting palpebral fissures[3,15,18] and proptosis were also reported in patients with LDS.[3,10,11,16,20,22,25,30] Down slanting palpebral fissures were documented in 20 out of 275 patients, while proptosis was documented in four out of 275 patients.

Eyelid

Eyelid ptosis has also been described in patients with LDS.[3,15,31] A total of three out of 275 patients with LDS were affected in the articles reviewed.

Table 1: A summary of the number of reports of various ophthalmic symptoms in patients with Loeys–Dietz syndrome from literature published in the past 5 years.[2,3,6-34]

Involved region	Specific symptom	Reported cases (out of 275 patients with LDS)
Craniofacial	Hypertelorism[3,6-28]	111
	Down slanting palpebral fissures[3,10,11,16,22,25,30]	20
	Proptosis[18,20]	4
	Ptosis[3,15,31]	3
Ocular motility	Strabismus[3,8,31]	8
	Amblyopia[3]	1
Refractive errors	Myopia[2,3,11,15,22,32]	9
	Hyperopia[3,6,16]	3
Cornea	Astigmatism[15,16,29]	25
	Corneal thinning[33]	8
	Corneal guttae[33]	2
Sclera	Blue sclerae[2,3,6]	5
Lens	Cataracts[35]	1
	Ectopia lentis[29,34]	2
Retina	Retinal detachment[22,29]	3

LDS: Loeys–Dietz syndrome.

Ocular Motility

LDS has been linked to features of ocular misalignment, including strabismus[3,8,16,22,27,29,31] and amblyopia.[29] Of the articles reviewed, eight out of 275 patients had strabismus, one of which also had amblyopia on exam.

Refractive Errors

Near-sightedness has been reported as part of the ophthalmic characteristics associated with LDS.[2,3,11,15,22,32] One study found that the eyes of patients with LDS were on average more myopic than the eyes of control patients, although not significantly more so.[29] Of the studies reviewed, nine out of 275 patients with LDS had documented myopia. Hyperopia has also been described in patients with LDS[3,6,16] and was found in three out of 275 patients.

Sclera

Blue sclerae have been linked to LDS.[2,3,6,9,33] In total, blue sclerae were documented in five out of 275 patients with LDS.

Cornea

Keratoconus has been associated with LDS.[29,35] Of the articles reviewed, two out of 275 patients with LDS were affected. In one study, although not significantly so, the eyes of patients with LDS had thinner central corneas on average than those of the control patients.[29] Decreased corneal thickness was also found in all three patients in an LDS case report;[34] the authors reference previous research that reported an average difference in thickness of 21 µm between patients with LDS mutations and control patients. This is important to study because decreased central corneal thickness is a risk factor for primary open angle glaucoma.[33] In another study, there were three

patients with corneal thinning, two of which also had corneal guttae.[34]

Astigmatism has also been described in patients with LDS.[15,16,29] Reports of astigmatism were found in 25 out of 275 patients in the articles reviewed.

Lens

Pseudophakia was found more commonly in the eyes of patients with LDS versus those of control patients (4.0% versus 0.8%) in one study,[29] although this may have been a coincidental finding considering the high incidence of cataracts in the general population. Lenticular opacities have also been reported in patients with LDS[22] and were noted in one out of 275 patients.

Some studies reported patients with LDS with ectopia lentis.[29,33] A total of two out of 275 patients with LDS had documented ectopia lentis. However, other studies did not find any cases in patients with LDS.[15,20]

Retina

Retinal detachments can occur in patients with LDS[22,29] and were described in three out of 275 patients with LDS in total. Two of these patients were diagnosed with familial exudative vitreoretinopathy (FEVR).[22] The prevalence of FEVR in LDS is uncertain, possibly because it is more likely to be missed than other ocular pathologies. However, the authors propose that the findings of both FEVR and aortic dilation may suggest LDS. Early FEVR identification is important to prevent progression of neovascularisation and blindness.[22]

Miscellaneous

Abnormality of the macular reflex was described in one patient.[2] Another patient experienced ptosis and anisocoria due to Horner syndrome, which was secondary to a subclavian artery aneurysm leak after stent graft placement.[36]

DISCUSSION

Studying the presence of ocular symptoms in LDS is important because of how it affects patient management. Previous studies have suggested a relationship between craniofacial abnormalities, including hypertelorism, and vascular events in patients with LDS, with more severe features being related to the first vascular event occurring at an earlier age.[24]

The most referenced ocular findings for LDS included hypertelorism (n=111), astigmatism (n=25), down slanting palpebral fissures (n=20), myopia (n=9), and strabismus (n=8). Interestingly, in one study, the eyes of patients with LDS had fewer cases of the following ocular issues compared to control patients: glaucoma, post-retinal detachment repair aphakia, cataracts, and iris transillumination defects.[29]

One limitation of this study was the small amount of available data. Connective tissue disorders can sometimes go undiagnosed; ophthalmic symptoms may not always be at the forefront of a patient's diagnosis or treatment due to their lower mortality risk. Also, some researchers may have difficulty attributing ocular symptoms to a disease process rather than genetic predisposition. For example, myopia is commonly found in patients with LDS, but it is also a very prevalent condition for healthy people as well, occurring in approximately 23% of the world population.[37] As a result, ocular symptoms may not be a focus in patient documentation and, in turn, less data are available for publishing.

Another limitation of this study was that not all articles had a specific prevalence for ocular manifestations. For example, one article reported hypertelorism in a category that also included other craniofacial features, such as cleft palate. As it was not possible to determine how many patients specifically had each symptom, this result was excluded from the frequency count. This may have led to the underreporting or overreporting of certain ocular symptoms.

An additional limitation of this study is related to the unstandardised measurement of certain ocular symptoms. Scleral discolouration and drooping eyelids are relatively subjective to diagnose. As such, there may be a bias in the

recording of these symptoms based on whether a patient has a connective tissue diagnosis already and whether these symptoms are being 'looked for'. Although hypertelorism can be measured, most of the articles reviewed did not report measurements against a standard number to define a patient as having hyper- or hypotelorism.

Future research could include a longitudinal, multicentre study that records ophthalmic conditions in patients with LDS prior to and after diagnosis. Having a large database of the ocular involvement of these conditions could promote earlier detection and potential treatments. Additionally, it may improve the understanding of how ophthalmic features, in addition to craniofacial features, may be related to vascular complications in these patients.

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Metabolic Syndrome and its Outcomes in Rheumatoid Arthritis: A Review

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Abstract

Metabolic syndrome is a cluster of health conditions linked to increased cardiovascular disease. It is found worldwide in increasing proportions due to the modern lifestyle. The increase is visceral fat leads to secretion of harmful proinflammatory cytokines that have deleterious effects on various tissues, chiefly the heart and vasculature. Rheumatoid arthritis is a systemic inflammatory disease that shares pathogenic mechanisms with the metabolic syndrome. Patients with rheumatoid arthritis suffer increased heart disease over and above traditional risk factors. They have an increased occurrence of metabolic syndrome that enhance the risk further. Metabolic syndrome occurs early in the course of rheumatoid arthritis, creating clinical opportunities for prevention and control. Patients with both conditions also have more severe disease, pain, poorer functional status, less remission rates, and suboptimal response to treatment. Treatment of metabolic syndrome should be aggressive, using a proactive approach. Lifestyle measures are a corner stone, and this should be coupled with optimal control of rheumatoid arthritis, blood pressure, and lipid levels. The concerted efforts by a multi-disciplinary team of rheumatologists, primary care physicians, and other providers will set the stage for reducing the increased cardiovascular morbidity and mortality in these two conditions. More prospective studies are the need of the hour in determining the roles of the risk factors and the effects of lifestyle changes and medications in reducing the impact of the metabolic syndrome and its contribution to the already burdened pathology of rheumatoid arthritis. This narrative review discusses the latest in the field and identifies the areas that need further research.

Key Points

1. An increase in visceral fats associated with metabolic syndrome leads to secretion of pro-inflammatory cytokines, with harmful effects on various tissues, including the heart and vasculature.

2. Overlap between rheumatoid arthritis and metabolic syndrome may result from shared pathogenic mechanisms. Patients with both conditions have more severe disease, pain, poorer functional status, lower remission rates, and suboptimal response to treatment, and particularly experience greater rates of atherosclerotic cardiovascular disease.

3. Screening for and treating metabolic syndrome are needed to reduce its impact on the pathology of rheumatoid arthritis and reduce the risk of cardiovascular disease associated with the pair of conditions.

INTRODUCTION

In 1988, Gerald Reaven coined the term Syndrome X. Reaven demonstrated that, in this syndrome, insulin resistance had a central role in increasing the risk of developing a cluster of conditions in people without diabetes. This cluster includes hypertriglyceridaemia; low high-density lipoprotein cholesterol (HDLc); small low-density lipoprotein (LDL) particle size; increased remnant lipoprotein; higher sympathetic nervous system activity; enhanced salt sensitivity; high plasminogen activator inhibitor-1; essential hypertension; and elevated serum uric acid.

Since then, the definition of this syndrome has undergone metamorphosis time and again. Subsequently, since insulin resistance was not present in all such instances, it was termed Metabolic Syndrome (Met-S).

Met-S has a higher incidence of atherosclerotic cardiovascular disease (ASCVD) and Type 2 diabetes (T2D), and consequent morbidity and mortality. T2D is an independent risk factor for ASCVD. Therefore, it is a priority for healthcare providers, policymakers, and patients to take appropriate measures to prevent and treat the condition. Various organisations such as the World Health Organization (WHO), International Diabetes Foundation (IDF), European Group for the study of Insulin Resistance (EGIR), American Association of Clinical Endocrinologists (AACE), and National Cholesterol Education Program's Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATP-III) have issued their criteria to define this condition resulting in differences in the reported prevalence of Met-S. The Endocrine Society practice guidelines 2019 have introduced 'Metabolic Risk' instead of 'Metabolic Syndrome'. Moving away from attempting to define a constellation of findings to qualify the Met-S to one of the identifying risk factors that increase ASCVD and T2D risks is welcome. It will help the practitioner look outside the box and examine traditional risks like family history of CVD, smoking, and LDL cholesterol, which are not part of the Met-S criteria. The European League Against Rheumatism (EULAR) has recommended a similar approach but with some differences.[1,2] Notwithstanding, the Met-S is still useful from a practice point of view (Tables 1 and 2). The presence of obesity is not a prerequisite for diagnosing Met-S because some patients who are not obese have the condition (metabolic obesity), and some are obese but do not have this conditon.[3] There is not much difference in the relative contribution of each of the components to Met-S. The risk for ASCVD persists even after eliminating T2D from the list. There is debate on the role of T2D in increasing this risk. We do not yet know whether the sum of the components is more than the individual components as far as the prognosis of Met-S is concerned.

ARE THERE OTHER MARKERS THAT PREDICT RISK?

Apart from the above, many other factors that depict ASCVD and T2D risks are receiving attention, and may be significant in some subpopulations. Still, there is insufficient evidence for their routine use in calculating ASCVD risk (Table 3).

Table 1: Endocrine Society criteria for metabolic syndrome in Asian and non-Asian populations.

Parameter	Recommendation
Age 40–75* and any three of the following	
WC (for non-Asian individuals)	Females: 88 cm or more Males: 102 cm or more
WC (for Asian individuals)	Females: 80 cm or more Males: 90 cm or more
Triglyceride	150 mg/dL or more
HDLc	Females: less than 50 mg/dL Males: less than 40 mg/dl
Blood pressure	Systolic: 130 mmHg or more Diastolic: 80 mm Hg or more
Glycaemic status	Fasting glucose: 100–125 mg/dL 2 hours post-75 g glucose load: 140–199 mg/dL HbA1c: 5.7–6.4% Drug therapy for pre-diabetes

*May evaluate patients younger than 40 years of age if clinically indicated.
HbA1c: glycated haemoglobin; HDLc: high-density lipoprotein-cholesterol; WC: waist circumference.

PREVALENCE OF METABOLIC SYNDROME

The prevalence of Met-S varies in different populations using different criteria. It can be explained by ethnic factors, as reported in many studies. The Asian populations have more fat for a given BMI. The upper limit of normal BMI in this population is 23 kg/m^2, and obesity is a BMI of 27 kg/m^2 or more. A waist circumference of 90 cm for men and 80 cm for women correlate with a visceral fat area of 100 cm^2. The visceral fat area values above 100 cm^2 have one or more obesity-related disorders such as hyperglycaemia, hypertension and dyslipidemia.[4-6] By using western norms, many Asian people will be branded as normal when they have Met-S. In a significant study, patients with rheumatoid arthritis (RA) had more fat for a given BMI than normal, similar to Asian people. They proposed a cut off of 23 kg/m^2 and 28 kg/m^2 for patients with RA who are normal and obese, respectively.[7]

Further testing is required in more patients with RA, but it does explain the result of a chronic inflammatory process.

WHAT CAUSES METABOLIC SYNDROME?

Lifestyle is key. A diet high in sugar, refined flour, red meat, and fats is causative, while a Mediterranean diet appears protective. Smoking is a risk factor that increases with the number of cigarettes smoked. Excess alcohol consumption also increases this risk. Physical inactivity increases body weight and BMI, enhances visceral fat deposition, alters lipid levels, decreases insulin sensitivity, and elevates blood pressure (BP). Genetic and epigenetic factors also influence these changes.

Visceral adipose tissue (VAT) is a metabolically distinct endocrine organ. It secretes several adipokines and cytokines. Adiponectin and omentin are anti-inflammatory, enhance insulin sensitivity, and modulate immune functions. In RA, adiponectin levels are reduced during active disease and correlate inversely with total cholesterol or HDLc index, blood glucose, and high-sensitivity C-reactive protein (hs-CRP) levels. This association is independent of BMI and hs-CRP levels and promotes atherogenesis.[8] IL-1β, IL-6, IL-8, TNF-α, MCP-1, and lipocalin-2

Table 2: European League Against Rheumatism (EULAR) criteria for cardiovascular risk assessment in rheumatoid arthritis and other inflammatory arthritides.

Disease activity should be controlled optimally in order to lower CVD risk in all patients with RA, AS, or PsA
CVD risk assessment is recommended for all patients with RA, AS, or PsA at least once every 5 years, and should be reconsidered following major changes in antirheumatic therapy
CVD risk assessment for patients with RA, AS, or PsA should be performed according to national guidelines and the SCORE CVD risk prediction model should be used if there are no national guidelines available
TC and HDLc should be used in CVD risk assessment in RA, AS, and PsA, and lipids should ideally be measured when disease activity is stable or in remission. Non-fasting lipids are perfectly acceptable
CVD risk prediction models should be adapted for patients with RA by 1.5 multiplication fact, if this is not already included in the risk algorithm
Screening for asymptomatic atherosclerotic plaques by use of carotid resound may be considered as part of the CVD risk evaluation in patients with RA
Lifestyle recommendations should emphasise the benefits for a healthy diet, regular exercise, and smoking cessation
CVD risk management should be carried out according to national guidelines in RA, AS, or PsA; antihypertensives and statins may be used as in the general population
Prescription of NSAIDs in RA and PsA should be given with caution, especially in patients with documented CVD or in the presence of CVD risk factors
Corticosteroids: for prolonged treatment, the glucocorticoid dosage should be kept to a minimum, and a glucocorticoid taper should be attempted in case of remission or low disease activity; the reasons to continue glucocorticoid therapy should be regularly checked

AS: ankylosing spondylitis; CVD: cardiovascular disease; HDLc: high-density lipoprotein-cholesterol; NSAID: non-steroidal anti-inflammatory drug; PsA; psoriatic arthritis RA: rheumatoid arthritis; TC: total cholesterol.

are pro-inflammatory. Excess VAT accumulation produces an imbalance in cytokine production favouring insulin resistance, elevated BP, adversely altered quantity and quality of lipid levels and consequently increases cardiovascular disease (CVD) risks. Manipulation of these cytokines is an attractive therapeutic target in managing Met-S.

RHEUMATOID ARTHRITIS AND METABOLIC RISK

RA and Met-S have inflammation as a core component in their pathogenesis. RA bites both the joints and the heart, whereas rheumatic fever licks the joints but bites the heart.

Met-S is higher in RA than in the general population in most studies.[9,10] However, studies from Mexico and Iran showed no differences in the former, and lower prevalence in the latter.[11,12] This may have been due to selection bias, medication effects, and other factors. A study from Singapore showed no change in outcomes in RA with Met-S, but revealed ethnic differences in CVD risks.[13] A study from Turkey revealed the presence of Met-S in naïve early RA.[14]

A study from North-East India included many treatment-naïve patients who had Met-S.[15] This confirms a common pathogenic pathway for both conditions and opens a window of opportunity for early intervention. In the KNHANES study, Met-S was lower in treated RA.[16]

Features of Metabolic Syndrome in Rheumatoid Arthritis

RA with Met-S has more dyslipidaemia and glucose abnormalities. Both RA with CVD and RA without overt CVD have Met-S. The latter have evidence of subclinical atherosclerosis as a result of increased carotid artery intima-media

Table 3: Other markers that could predict risk.

Uric acid
Alanine transaminase (surrogate for fatty liver)
Homocysteine
Insulin
Proinsulin
Fibrinogen
Free fatty acids (marker of insulin resistance)
hs-CRP (a marker of an inflammatory state)
Apolipoprotein B
Lipoprotein(a)
Leptin
Adiponectin
PAI-1
Proinflammatory cytokines
Microalbuminuria in subjects without diabetes (a surrogate marker for endothelial dysfunction)
Fat content quantification in the liver or muscle using magnetic resonance spectroscopy
Genomic markers for T2D or ASCVD

ASCVD: atherosclerotic cardiovascular disease; hs-CRP: high-sensitive C-reactive protein; T2D: Type 2 diabetes.

thickness (cIMT) and characteristic findings in cardiac MRI.[17-19] Met-S is higher in longstanding RA, individuals who are older, smokers, males, and post-menopausal females, and those with higher Disease Activity Score-28 (DAS-28) scores.[20,21] Males with RA and Met-S had higher individual components of the Met-S than females. Patients with RA and Met-S had lower vitamin D levels.[22] The coronary artery calcium scores are higher in RA, and Met-S aggravates this.

Patients with both conditions have more pain, increased physical inactivity, poorer functional status, and resistance to traditional treatments. Met-S added to RA leads to lower remission rates.[23]

Cardiovascular Risks in Rheumatoid Arthritis

Only a quarter of patients with RA received antihypertensive treatment for hypertension; among those patients, only half had optimal control of systolic BP until a few years ago. The situation has changed, and many patients with RA and hypertension now receive optimal treatment. Elevated hs-CRP, glucocorticoids, and non-steroidal anti-inflammatory drugs aggravate hypertension. Hypertension increases mortality from myocardial infarction by 80% in patients with RA. RA independently raises the risk for ASCVD, as diabetes does. The EULAR guidelines advise that the ASCVD risk calculated from traditional risk calculators be multiplied by 1.5 for patients with RA.

Since the conventional risk factor algorithms underestimate the risk for ASCVD in RA, there is a

role for non-invasive tools like cIMT measurements using carotid ultrasound for risk assessment (Table 2).[24] This risk is over and above that contributed by conventional factors. So, patients with RA have double jeopardy. As noted earlier, Met-S is higher in RA and is detected even in the early stages.

CVD in RA goes beyond the traditional risk factors. Patients with RA have a 50% increase in CVD, and almost twice as many acute coronary events and strokes as the average population with similar traditional risks, as shown in the Nurses' Health Study. In some studies, CVD risks predate the first joint symptoms of RA. In patients with RA who have cardiac symptoms but negative non-invasive tests, cardiac MRI reveals abnormalities in cardiac function. Burggraaf et al.[25] followed RA patients both with and without Met-S, and found that treatment for RA did not prevent the subclinical progression of atherosclerosis as measured by cIMT. This not only shows the aggravating role of Met-S in RA, but also that treatment of RA alone is insufficient, and that Met-S has to be dealt with individually. When T2D and RA occurred together, ASCVD was double, and markers of Met-S (hyperlipidaemia, hypertension) increased.[26]

Biomarkers Contributing to Enhanced Metabolic Syndrome and Cardiovascular Disease in Rheumatoid Arthritis

IL-6, IL-1β, and TNF-α are key in RA and ASCVD.

TNF-α increases dyslipidaemia, enhances oxidised LDL, enhances foam cell formation, impairs the antioxidant effects of high-density lipoprotein (HDL), and compromises endothelial integrity. It reduces nitric oxide and thrombomodulin and promotes coronary calcification and a prothrombotic environment.

IL-1β increases the expression of adhesion molecules that promote atherosclerosis.

Other contributors to increased morbidity include increased oxidative stress, citrullination of LDL rendering it more atherogenic, activation of the cluster of differentiation 40–cluster of differentiation 40L axis pathways, which enhance inflammation and fibrosis and lead to plaque instability, rupture, thrombosis, and coronary events.

Serum amyloid A is high in RA, binds to HDL, decreases its anti-oxidative functions, and promotes ASCVD.

Nuclear factor κ-light-chain-enhancer of activated B cells is key to inflammation in RA. It elevates IL-6, IL-17, IL-18, IL-33, TNF-α, hs-CRP, vascular cell adhesion protein 1, and intercellular adhesion molecule 1. Many of these stimulate multiple pro-inflammatory pathways simultaneously and produce a synergistic effect that is far greater than the sum of their contributions. The results are devastating atherogenesis and thrombosis.[27]

Epicardial fat is VAT, increased in RA with Met-S. Research has shown that increased epicardial fat volume produces dysfunctional adipocytes that secrete pro-inflammatory cytokines that promote atherosclerosis and coronary calcification.[28] Higher intermuscular and intramuscular fat correlated with levels of VAT and Met-S.[29]

ASSESSMENT OF RISK FOR METABOLIC SYNDROME IN RHEUMATOID ARTHRITIS

Subclinical atherosclerosis demands a proactive approach to Met-S to prevent CVD events and silent myocardial infarction. Screening for Met-S should be routine in the medical evaluation of patients with RA. RA specific CVD risk assessments are available. A Korean pilot study found the Expanded Risk Score in Rheumatoid Arthritis (ERS-RA) helpful in predicting subclinical atherosclerosis. However, a validation analysis of data from seven countries using several RA specific risk scores for estimating CVD risks did not find any superior methods to traditional risk scoring systems. In surveys of practising rheumatologists in the USA, <40% addressed CVD risks in their patients. This gap has to be closed to achieve any meaningful decrease in CVD. An alternative to this is the education and involvement of primary care providers. Another alternative is a multi-disciplinary clinic. It should comprise rheumatologists, endocrinologists, cardiologists, radiologists, and primary care providers with provider-specific tasks.

Individual Tests for Metabolic Syndrome

Anthropometry

A waist circumference (WC) is measured (Table 1). The WC is a useful marker for visceral adiposity and Met-S. It is easy to perform in the physician's office and takes very little time. If accurately measured, it will ease risk classification and intervention. Alternatively, an index derived from the WC divided by height is also useful and has a good correlation with markers of Met-S. It has various terms; the index of central obesity, weight-to-height ratio, or weight-to-stature ratio, and the normal cut off is 0.5. Other measurements like the visceral adiposity index and the lipid accumulation product are yet to be validated.[30-32]

Blood pressure measurements

Standard protocols for accurate measurements of BP remain valid when evaluating patients with RA and Met-S (Table 4).

Lipid profile

A fasting sample will yield the total and HDL cholesterol and triglyceride (TGL), which vary in the EULAR guidelines.

Glycaemic status

Fasting glucose, a two-hour post 75 g glucose load test, or an HbA1C can be used, which varies in the EULAR guidelines.

If three or more components of Table 1 are detected, the height, weight, BMI; the LDL cholesterol, and non-HDLc are measured.

If the TGL is more than 400 mg/dL, the calculated LDL is inaccurate and LDL is directly measured.

The patient should be screened for smoking, a family history of ASCVD, and be enrolled in a programme for lifestyle modifications (Table 5).

For those who have only one or two components of Table 1, after the additional screening, lifestyle modifications are done as above, and periodic monitoring in intervals of 1–3 years is mandatory depending on circumstances.

WHAT FACTORS ARE SPECIFIC TO METABOLIC SYNDROME IN RHEUMATOID ARTHRITIS?

The above protocol is applicable in patients with RA with Met-S, but existent studies are cross-sectional, and evidence-based studies are lacking. There are handicaps in RA that may interfere with the smooth implementation of a lifestyle program. Active disease may cause fatigue, pain, restricted joint mobility, and in later stages, deformities. Therefore, it is imminent that effective treatment of RA and Met-S management must go together. A pain-free joint with a good range of motion will make an exercise programme most effective.

Table 4: Standard protocols for taking accurate blood pressure measurements.

The sphygmomanometer should be of a standard make and well calibrated
The patient should have rested for at least 5 minutes and not taken coffee or smoked 30 minutes before the measurements are taken
The preferable sitting position is one where the arm is resting comfortably at heart level
The BP cuff should cover at least 80% of the arm circumference
Both palpatory and auscultatory BP measurements are obtained
Korotkoff sounds I and V are used for calculating the systolic and diastolic measurements, respectively
A minimum of two measurements are taken several minutes apart and averaged
The BP is measured in both arms and the higher reading is taken
The patient or provider should refrain from talking during the procedure

BP: blood pressure.

Table 5: Lifestyle modifications.

Heart healthy diet with calorie restriction to achieve a 5% weight loss
Salt restriction
Smoking cessation
Moderation of alcohol to prescribed limits
Structured exercised programme and reduction of total sedentary time
BP targets, with above modifications and, if needed, medication
Lipid targets, with above modifications and, if needed, medication

BP: blood pressure.

However, all is not lost if handicaps already exist. It is where experts in physical medicine can be of help in structuring an individualised exercise program. An example is water aerobics for patients who experience pain and restricted mobility when doing regular exercises.[33]

The disease activity or treatment of RA with particular agents may alter the values of the glucose or lipid measurements. It will not only change the Met-S classification status, but may render the treating physician to be lax on instituting measures to prevent or treat ASCVD. An example is a patient in an inflammatory state with decreased LDL, HDL, and TGL levels (lipid paradox) who fails to qualify as Met-S. The same patient will meet the criteria for Met-S when assessed after treatment once the inflammation has reduced and lipid levels have risen to their 'true' values. Treatment with hydroxychloroquine (HCQ) decreases glucose levels and RA disease activity. A patient with RA under treatment with HCQ will not meet the criteria for Met-S during treatment. In such instances, the risk for coronary events remained elevated despite normal lipid levels. An elevated hs-CRP, which is a risk for ASCVD, could cause decreased lipids. Studies from different sites have revealed varied conclusions.

LIFESTYLE MODIFICATION AND ITS IMPACT ON RHEUMATOID ARTHRITIS OUTCOMES

Smoking

It is well established that smoking increases CVD in the general population. In RA, smoking increases antibody production (rheumatoid factor, anti-citrullinated antibody), worsens the disease, diminishes gains from therapy, and increases ASCVD morbidity and mortality. Smoking cessation should receive top priority to reduce RA activity and ASCVD. García-Chagollán et al.[34] showed that in RA with Met-S, smoking correlated positively with higher disease activity, higher levels of hs-CRP, and RF yielding evidence that treatment of Met-S can decrease RA and ASCVD.[35]

Exercise, Weight Loss, and Dietary Patterns

Physical inactivity is inversely related to CVD events and increasing physical activity decreases CVD deaths significantly. Patients may have additional handicaps such as pain, fatigue, joint stiffness, deformities, and inertia that hinder an exercise programme. Successful exercise programmes in patients experiencing these symptoms result in significant improvements in BP, lipids, hs-CRP, homocysteine, plasminogen activator inhibitor-1, and endothelial function, apart from musculoskeletal benefits.[36] Improved cardiopulmonary fitness using aerobics and resistance will aid in successful participation in

an exercise programme and promote quality of life.[37]

A heart-healthy diet goes hand-in-hand with an exercise programme. Three landmark studies (Da Qing study, Finnish Diabetes Prevention Study, and Diabetes Prevention Program) on the effect of diet, weight loss, and increased physical activity in patients with elevated metabolic risk (Met-S) consistently showed improvements in BMI, WC, BP, lipids, hyperglycaemia, and ASCVD. More intense exercise and calorie restriction had improved outcomes. Dietary patterns (Mediterranean style, which has anti-inflammatory effects reducing pro-inflammatory cytokines) and salt restriction showed superiority to conventional western diets. More importantly, the results of such interventions were persistent even many years after the interventions, confirming 'metabolic memory'.[38-40]

Although these results were on patients without RA, they can extrapolate to RA.

Walrabenstein et al.[41] reported favourable outcomes of a whole food plant diet in RA. Based on encouraging results, they outlined a prospective extension study integrating exercise and stress reduction with whole food plant diet for two years on the natural history of established (Arm-1) and new (Arm-2 in patients who are anti-citrullinated antibody-positive without clinical disease) RA. The results will answer many questions on the roles of lifestyle interventions in RA, ASCVD, and Met-S.[41]

MEDICATIONS AND EFFECTS ON RHEUMATOID ARTHRITIS AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE OR METABOLIC SYNDROME

Lower disease activity in RA decreases ASCVD risk factors and CVD events. With TNF-α inhibitors, optimal disease control decreases ASCVD significantly, but symptom control alone does not. This agent improved insulin sensitivity, decreased oxidised LDL, improved pulse wave velocity, reduced arterial stiffness, and reduced myocardial infarction significantly.[42]

Methotrexate is often the first-line therapy for RA. It decreases harmful cytokines, improves the antioxidant function of HDL, prevents foam cell activation, enhances the scavenging of free radicals, improves insulin-mediated glucose transport, and restores endothelial function. Met-S was lower in RA treated with methotrexate.[43] There is a 20% reduction in the composite CVD event rates from pooled data from ten studies.[44]

HCQ has many benefits in RA. It improves insulin sensitivity and lipid profile. It suppresses IL-1, IL-6, and TNF-α production. It prevents the proliferation of T lymphocytes and toll-like receptors, enhances endothelial function, creates an antithrombotic milieu, and consequently reduces ASCVD.[42,45,46]

The IL-6 inhibitor tocilizumab makes HDL more anti-atherogenic. In addition, it improves insulin sensitivity, even in patients with RA but without diabetes.[47,48]

There were concerns about the LDL increase with tofacitinib (a JAK inhibitor). The STAR-RA trial recently advised caution in patients with RA and CVD risks.

Many studies have benefits of statins in RA. Atorvastatin fared better than simvastatin, showing a reduction in LDL, TGL, and hs-CRP; an increase in HDL; and improvement in DAS-28 scores. The pleiotropic effects of the statins effectively reduced RA activity and ASCVD risk.[49]

The deleterious effects of glucocorticoids are well known. Although they reduce inflammation, they cause and perpetuate Met-S: a higher dose and longer duration are associated with more side effects. The EULAR guidelines advise restricted use.

CONCLUSION

Patients with RA are at high-risk for ASCVD. This risk is well above the traditional risk factors.[50] Met-S is increased in RA and contributes to a higher disease burden. It occurs early in its course and is associated with less remission. It is higher in males and post-menopausal females, with older age, smoking, increased disease activity, and suboptimal treatment. Subclinical atherosclerosis is a hallmark of RA, and Met-S aggravates it. RA

and Met-S have common inflammatory aetiologies. Patients with should be screened for metabolic risk early, during initial diagnosis and should look outside the Met-S box. Treatment of individual metabolic risk factors is in addition to optimal control of RA. Hypertension in RA worsens ASCVD risk and events and is not well managed currently by practitioners, especially in developing countries. Many anti-rheumatic agents reduce ASCVD and the contributing factors to Met-S. Lifestyle modification is the first line of management of Met-S in RA. More prospective studies examining the specific role of Met-S in RA and the means to reduce it are needed. The education of primary care providers on the optimal care of Met-S in RA and the institution of multi-disciplinary clinics are the need of the hour.

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A Self-Resolving Flare of Psoriasis after COVID-19 Vaccination

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Abstract

Flares of autoimmune disorders have been rarely reported after COVID-19 infection as well as vaccinations. The authors report a case of psoriasis flare after COVID-19 vaccination, which was successfully treated with topical steroids. This case illustrates that although autoimmune disease flares might be seen post-vaccination, they are usually mild and self-resolving. Therefore, based on overall safety and efficacy, COVID-19 vaccination is strongly encouraged in vulnerable patient populations.

Key Points

1. There have been rare reports of exacerbations of rheumatic and musculoskeletal diseases after COVID-19 vaccination.
2. Although autoimmune disease exacerbations might be seen post-vaccination, most are mild and self-resolving.
3. Given the overall safety and efficacy of COVID-19 immunisation, vaccination is strongly encouraged in vulnerable patient populations.

FLARE OF PSORIASIS AFTER COVID-19 VACCINATION

Case Presentation

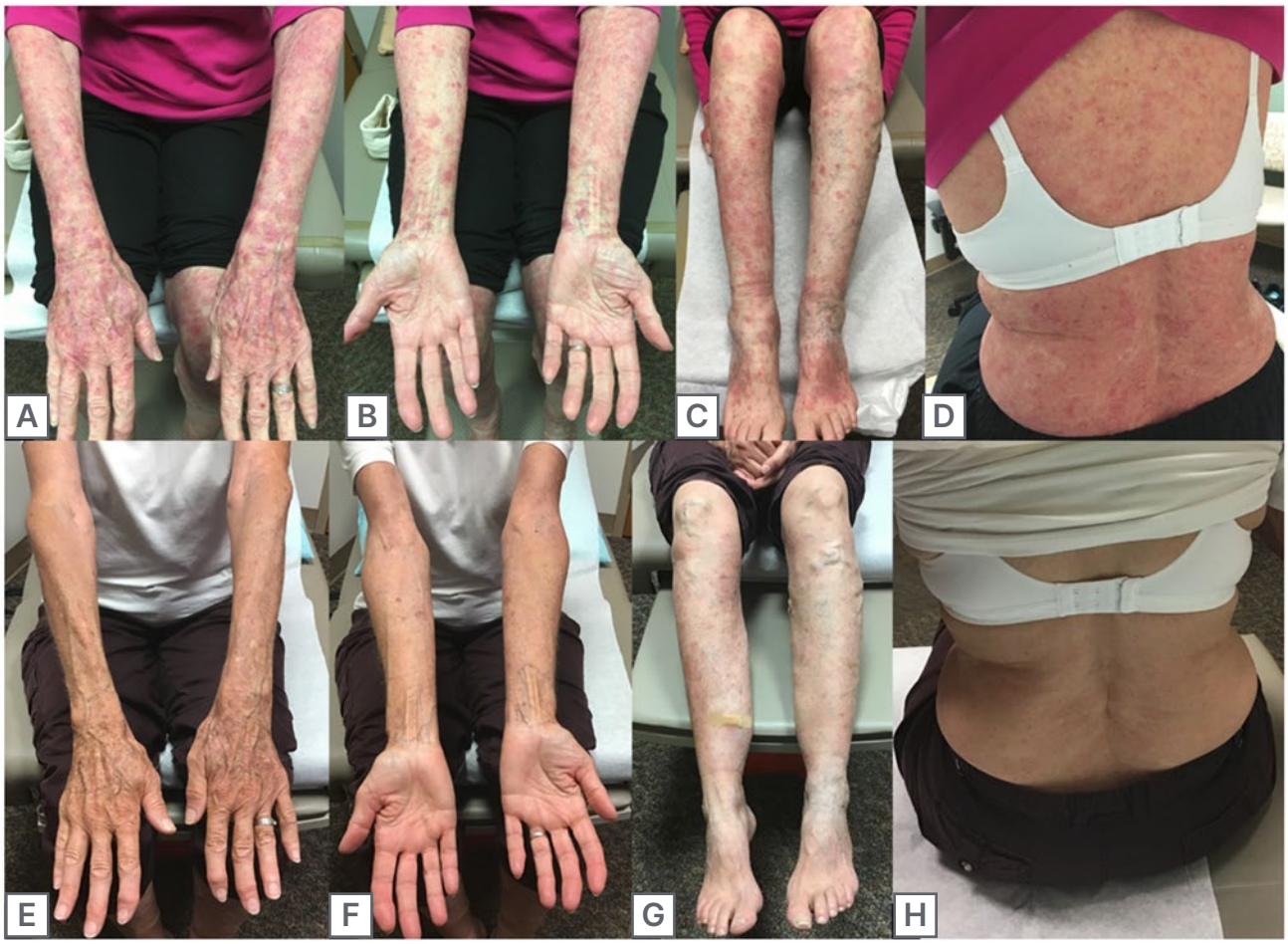
A 63-year-old female with history of psoriasis, degenerative disc disease, and osteoarthritis of the hands and knees presented with worsening skin psoriasis. They were diagnosed with plaque psoriasis 45 years ago, well-controlled with as-needed topical corticosteroid ointment. Their last exacerbation of psoriasis was more than 5 years ago and had resolved with topical management. Two weeks after

receiving the second dose of the BNT162b2 mRNA vaccine (Pfizer, New York City, New York USA, and BioNTech, Mainz, Germany), the patient developed itchy erythematous scaly rashes on their extremities, chest, abdomen, and back. The physical examination revealed erythematous pustular plaques all over the body. (Figure 1A–D) They were advised to use topical triamcinolone 0.1% cream twice a day, with a plan to initiate systemic immunosuppressive therapy for psoriasis. However, before initiating immunosuppressive therapy, their rash started resolving, and completely resolved spontaneously within 6 weeks of onset. (Figure 1E–H). On evaluation 3 months after the initial presentation, the patient continued do well and did not have any more psoriasis exacerbations, despite no topical or systemic therapy.

Discussion

COVID-19 can cause immune-overactivation and hyperinflammation, and has been associated with exacerbation of rheumatic and musculoskeletal diseases (RMD) as well as new incident RMDs.[1] Concerns about autoimmunity caused by vaccines due to molecular mimicry exist, with rare reports of RMD flare after COVID-19 vaccinations.[2-4] Cases of new-onset psoriasis and exacerbation of psoriasis after COVID-19, as well as COVID-19 vaccinations, have been recently reported.[5-8] Fortunately, similar to this

Figure 1: Physical examination of patient revealing erythematous pustular plaques, which resolved spontaneously.



Erythematous scaly pustules and plaques 2 weeks after COVID-19 vaccination on **A)** dorsal arms and hands; **B)** volar arms and hands; **C)** anterior legs; and **D)** back. Complete resolution of the rash 6 weeks later as shown on the **E)** dorsal arms and hands; **F)** volar arms and hands; **G)** anterior legs; and **H)** back.

case, most cases were successfully treated with topical treatment, with few requiring systemic therapy. The findings of this report align with the currently available clinical data and illustrates that though vaccines may increase the risk of RMD flares, flares are usually mild and self-resolving. Given the overall safety and efficacy of COVID-19 immunisation, the proven benefits of vaccinating vulnerable patients outweigh the potential theoretical risk of disease flare and vaccination shall be strongly encouraged.

Patient's Perspective

The patient is enthusiastic about sharing their experience and appreciates an opportunity to help the medical community. They want their case to be a reassuring example for those who have concerns about the COVID-19 vaccines, and strongly encourage everyone to get vaccinated for COVID-19.

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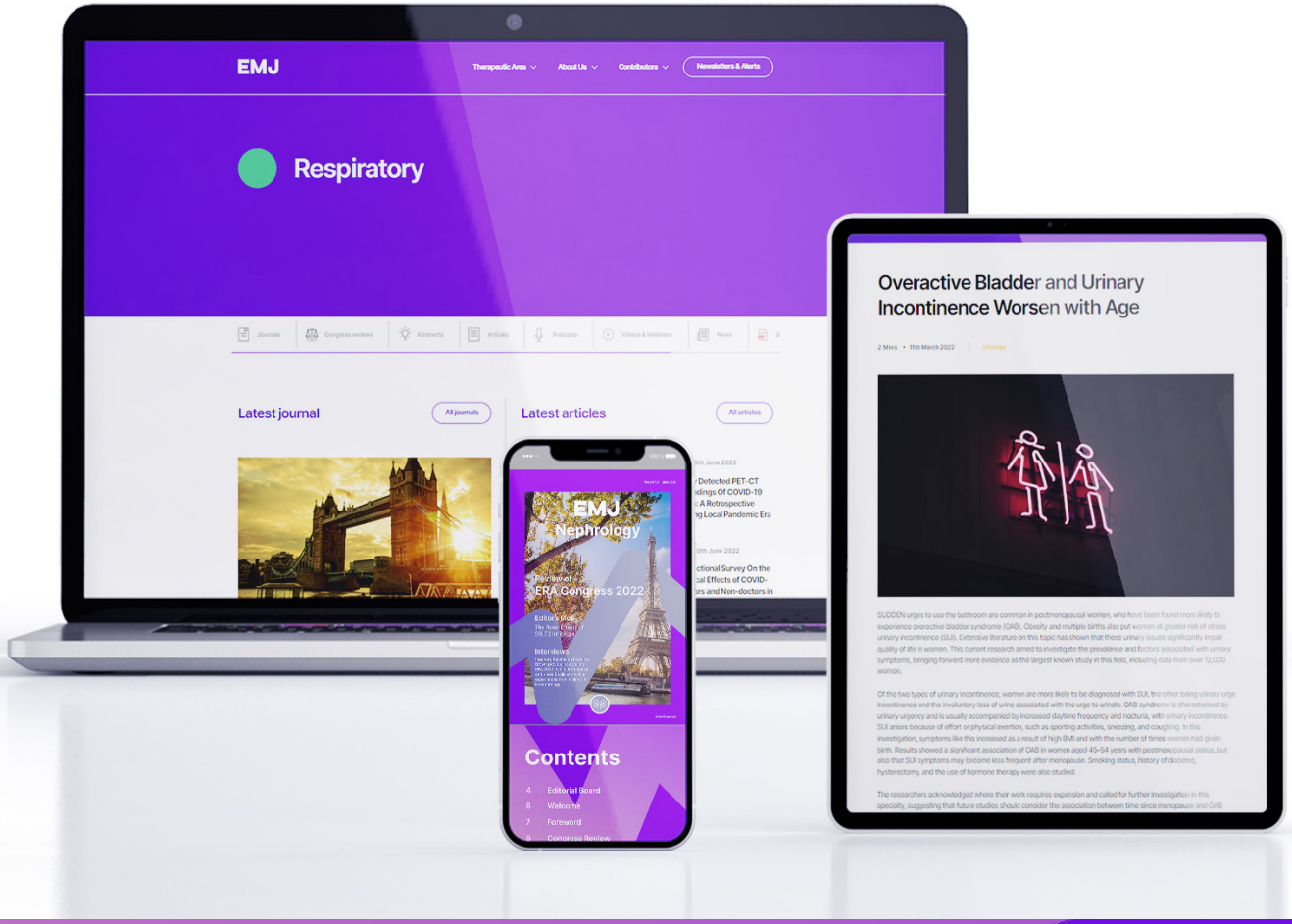

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