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EULAR 2021

EDITOR'S PICK

Management of Pregnancy in Rheumatic Disease

INTERVIEWS

Interviews with Christopher Edwards and Karen Walker-Bone

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Editorial Board

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Aims and Scope

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EMJ Rheumatology 8.1

Welcome

Dear Readers,

We are delighted to present to you our latest issue of *EMJ Rheumatology 8.1*! This eJournal explores the most important rheumatology developments through a series of captivating and exclusive interviews and educative articles from experts within the field. You will also find a review of the European League Against Rheumatism (EULAR) Congress 2021. At EMJ, we want to continue to promote ground-breaking research and innovation with this open-access latest issue of *EMJ Rheumatology 8.1*.

Included in this issue are six peer-reviewed journals on topics including an update on the epidemiology of axial spondyloarthritis and the clinical manifestations and diagnosis of Behçet's Syndrome. The Editor's Pick for this issue is the review paper "Management of Pregnancy in Rheumatic Disease" where Sinead et al. articulately discuss this complex subject area and the current American College of Rheumatology (ACR) guidelines on pregnancy.

We have an exciting and comprehensive review of the EULAR Congress 2021, and despite a move to the virtual, expertly covering a broad spectrum of rheumatic diseases via a series of high-quality lectures, presentations, and special interest group sessions. In addition to this, we had the great opportunity for Congress interviews with Joan Bathon from the EULAR Scientific Programme Committee and Ricardo Ferreira, Chair of EULAR Committee of Health Professionals in Rheumatology.

We had the pleasure of interviewing Christopher Edwards and Karen Walker-Bone on their ongoing passion for rheumatology, the driving forces behind their work, and the effects of COVID-19 on their field in the last year. We are extremely pleased to offer a broad range of abstract summaries on topics including atherosclerosis burden in rheumatoid arthritis, association between environmental air pollution and rheumatoid arthritis, diffuse cutaneous systemic sclerosis, Pneumocystis jjiroveci pneumonia, TNF-α antagonists and tocilizumab in Takayasu arteritis, and more!

I would like to take the opportunity to acknowledge and thank the Editorial Board, authors, and interviewees and to the EMJ publishing team for their hard work in bringing this research to you. We sincerely hope that you enjoy reading this latest issue of *EMJ Rheumatology 8.1*.

Spencer Gore

Chief Executive Officer, EMG-Health

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Foreword

Dear Colleagues,

It is my pleasure to present this issue of *EMJ Rheumatology*. The main theme is axial spondyloarthritis (AxSpA), including ankylosing spondylitis (AS), focusing on clinical and diagnostic aspects.

The Editor's Pick is the review paper 'Management of Pregnancy in Rheumatic Disease' by Sinead et al. While disease activity in some rheumatic and musculoskeletal diseases improves during pregnancy, it worsens in others. The complex issue of drug treatment during pregnancy is reviewed with current American College of Rheumatology (ACR) guidelines on pregnancy in rheumatic diseases.

Detecting early inflammation in AxSpA is key to early diagnosis and intervention, to achieve remission and avoid progression to spinal syndesmophytosis and disability. Wu et al. review the use of nuclear medicine bone scan with quantitative sacroiliac scintigraphy (QSS) as a sensitive indicator of inflammation in the sacroiliac joints; the use of QSS is a good screening tool for early detection of AxSpA and could be used to monitor drug responses.

The diagnosis of Behçet's can be difficult. Pathophysiologically, it sits at the interphase between auto-inflammation and autoimmune inflammatory-mediated disorders. Beça et al. discuss the current state of the art for clinical manifestations and diagnosis of Behçet Syndrome.

Infections can drive inflammation in AxSpA and gut microbiota may play a role in the overlap between AxSpA and Crohn's disease. Stebbings et al. discuss the co-inheritance of these diseases and the existence of a plethora of shared genetic risk loci that have been revealed by analysis of genealogic databases and genome-wide association studies.

Early detection and diagnosis facilitates early therapeutic intervention and good clinical outcomes in patients with AxSpA. Islam et al. report their study on a Bengali inflammatory back pain tool and its performance against the new Assessment of SpondyloArthritis International Society (ASAS) expert criteria, in radiographic axSpA and non-radiographic axSpA.

Finally, MacGearailt et al. present an overview of axial features, peripheral manifestations, associated comorbidities, and disease outcome tools, and provide a summary of general principles of treatment and patient education in the management of individuals with AxSpA.

In conclusion, the boundaries of knowledge of AxSpA continue to expand. As Editor-in-Chief, I thank all the contributors to this issue, and the authors and peer-reviewers for committing their time despite the COVID-19 related pressures.

Prof Ian C Chikanza

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

To see is to believe? Guidance on using imaging to optimize patient care in psoriatic arthritis

Learnings from the Janssen-Sponsored Satellite Symposium at the EULAR 2021 Virtual Congress on 2 June 2021

With speakers:
Dennis McGonagle, Mikkel Østergaard, and Alen Zabotti

janssen Immunology
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

1 Psoriatic arthritis (PsA) characteristics and the role of the IL-23 pathway

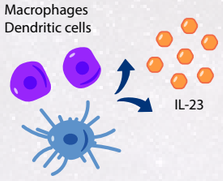
PsA manifestations include:[1]

- Peripheral joint disease
- Dactylitis
- Enthesitis
- Axial joint disease
- Psoriasis
- Nail psoriasis

Common genetic aspects are indicators of the role of the IL-23 pathway in spondyloarthritis (SpA), PsA, and psoriasis[2]

Antigen-presenting cells

Monocytes
Macrophages
Dendritic cells

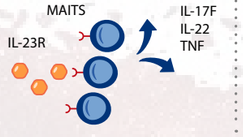


Possible genetics associated with IL-23 induction in spondyloarthritis (SpA)

- CARD9 (dectin-1 fungal stimulation)
- DITRA (IL-36 signalling)
- HLA-B27 (protein misfolding)
- IL-13

IL-23R cells

Th17
Tc17
ILC3
MAITS



Genetics associated with IL-23 response in SpA

- IL-23R
- IL-12p40
- IL-6R
- IL-13
- TYK2

Therapy on the IL-23 pathway in PsA

Evidence shows that **blockade of the IL-23 pathway inhibits the intracellular and downstream signalling of IL-23,** and may result in significant improvements in:

- ACR 20, 50, and 70 responses[3]
- Dactylitis resolution[3]
- Enthesitis resolution[3]

2 The role of imaging in PsA disease management

Conventional radiography (x-ray)

Conventional radiography is the most common imaging modality for PsA[4]

Advantages of x-ray imaging:[4]

- Fast
- Accessible
- Relatively inexpensive
- Reliable

However, conventional radiography is limited by[4]:

- Capability for 2D images, only
- Limited usefulness in imaging soft tissues
- Inability to detect early/small erosions

Magnetic resonance imaging (MRI)

Similar to ultrasound (US), MRI can visualize bone erosion, synovitis, enthesitis, and dactylitis, as well as:[5]

- Bone inflammation (incl. location)
- Progression of bone damage
- Presence of axial involvement
- Inflammatory load

MRI is the imaging method of choice for axial PsA diagnosis and monitoring[5]
Whole-body MRI also potentially allows for simultaneous assessment of axial and peripheral disease manifestations[5]

US

Can be used to visualize the following pathologies:[6]

- Synovitis
- Enthesitis
- Dactylitis
- Soft-tissue oedema
- Bone erosion
- New bone formation

US is more sensitive than clinical examination in identifying enthesitis and synovitis[7,8]

3 US in clinical practice

US and diagnosis of early PsA

Active synovio-entheseal abnormalities can be identified via US in clinically asymptomatic patients with psoriatic disease[9]

According to the **EULAR guidelines:**

- Clinically identified arthritis can be confirmed via US[10]
- US is sensitive in detecting synovitis in the knee and small joints[10]

If peripheral SpA is suspected, US can be used to detect peripheral enthesitis to support diagnosis[10]

If musculoskeletal US criteria for active synovitis or active enthesitis are used to define subclinical PsA,

40% of psoriatic patients show subclinical PsA[11]

Patients with psoriasis with inflammation or structural damage were nearly

4× more likely to develop PsA within 1–2 years[12]

US can also be used in clinical practice to visualize the underlying mechanisms of PsA, including:[12]

- Peritendon extensor inflammation
- Flexor tenosynovitis
- Dactylitis scores

References: 1. Belasco J, Wei N. Rheumatol Ther. 2019;6:305-15. 2. Bridgewood C, et al. Immunol Rev. 2020;294:27-47. 3. Mease PJ, et al. Lancet. 2020;395:1126-36. 4. Felbo SK, et al. Clin Exp Rheumatol. 2018;36 suppl 114 24-34. 5. Poggenborg RP, et al. Ther Adv Musculoskelet Dis. 2011;3:43-53. 6. Kaeley GS, et al. Arthritis Res Ther. 2020;22:1; 7. Gutierrez M, et al. Semin Arthritis Rheum. 2011;40:407-12. 8. Naredo E, et al. Rheumatology (Oxford). 2011;50:1838-48. 9. Gisondi P, et al. Ann Rheum Dis. 2008;67:26-30. 10. Combe B, et al. Ann Rheum Dis. 2017;76:948-59. 11. Zuliani F, et al. Clin Exp Rheumatol. 2019;37:593-9. 12. Zabotti A, et al. Poster presented at EULAR 2021; abstract POS0145.

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Congress Review

Review of the European Alliance of Associations for Rheumatology (EULAR) 2021 Virtual Congress

Location: EULAR 2021 virtual congress

Date: 2nd–5th June 2021

Citation: EMJ Rheumatol. 2021;8[1]:12-24. Congress Review.

Virtual again... once more the European Alliance of Associations for Rheumatology (EULAR) took the decision to hold their prestigious annual conference online in the face of the continuing COVID-19 pandemic. Originally organised to be hosted in Paris, France, the online conditions were no sanction to the congress as EULAR perfectly demonstrated rapid and effective adaptation to the 'new normal' of virtual congresses and online learning. The meeting resumed its full agenda and provided a seamless platform for all attendees to engage in sessions and meetings.

The Opening Plenary Session was given by Iain McInnes, EULAR President, who welcomed the virtual audience to EULAR 2021 and shared the objective of EULAR: "We seek to deliver world-class education, to provide penetrating and effective advocacy to our political classes, to offer empathetic and comprehensive support to patients, and to sustain the research efforts that will ultimately lead to cures for people with rheumatic diseases." He went on to introduce keynote speaker Mark Pollock, who gave an inspiring talk on building resilience against trials and tribulations as he, as a blind person, sadly fell and sustained an injury causing him to become permanently paralysed. "You have a decision to be a soloist or a collaborative person. Being blind and paralysed is a big challenge for the quality of life," shared Pollock. This challenge led him to collaborate with the 'Project Walk' paralysis recovery centre. "We should always build on resilience and collaborate. An attitude that is important to the world of people working together in fighting rheumatic diseases... The really big breakthroughs happen when we decide to be collaborators."

The highlights from the exciting and extraordinary 2021 Scientific Programme were delivered by Loreto Carmona, EULAR 2021 Scientific Programme Chair, one of the global leaders in clinical and epidemiological rheumatology research and the person responsible for orchestrating the programme. The Scientific Programme

"We seek to deliver world-class education, to provide penetrating and effective advocacy to our political classes, to offer empathetic and comprehensive support to patients, and to sustain the research efforts that will ultimately lead to cures for people with rheumatic diseases."

was rich in diversity. It included debate sessions on topics such as remote rheumatology and publication ethics; 'innovation stations' on topics such as 'fake news', drug development with a team from the European Medicines Agency (EMA), and new techniques for research on rheumatoid arthritis and spondyloarthritis, and lesser-known conditions such as Lyme disease; and workshops for practical skills. After laying out the programme, Carmona highlighted: "In each session of the congress, you will have something specifically for you. Please enjoy it."

McInnes then turned to Hendrik Schulze-Koops, Chair of the EULAR Abstract Committee, who presented the EULAR Abstract Awards. Schulze-Koops commended the success of science in spite of the pandemic: "It is wonderful to have seen so many contributions from people all over the world that work hard on rheumatology research and contribute to the success of EULAR. We had more than 3,000 abstracts submitted to the EULAR meeting, which were then divided into categories and scored by more than 100 people." Abstracts could be submitted under poster presentations, poster tours, and selected presented abstracts. The abstract categories were The Future in Rheumatology (for undergraduates), Health Professionals Rheumatology, People with Arthritis/Rheumatism in Europe (PARE), FOREUM, Basic Science, and Clinical Science, the winners for which included Giovanni Adami, Italy, whose abstract summary can be found in this journal issue.

Annamaria Iagnocco, EULAR President-Elect, shared her remarks on the future of EULAR and where she expects the direction of EULAR

to traverse under her upcoming leadership and guidance. "The RMD community has the potential to adapt to new challenges and to look into the future. The EULAR family is a team of people working together... In 2022 we will celebrate our 75th anniversary in Copenhagen, Denmark."

Awards were bestowed upon those who have shown astounding commitment to the discipline, whether in research, clinical science, or activities in EULAR. The winners of the Meritorious Awards were Maxime Dougas, France, and Josef Smolen, Austria, who Iagnocco praised for serving rheumatology in national and international prestigious roles. Honorary Membership Awards were given to Rikke Helene Moe, Norway, and Dieter Wiek, Germany, who have shown outstanding loyalty in achieving the objectives of EULAR. Finally, the Edgar Stene Prize was awarded to a person with rheumatic or musculoskeletal disease who had submitted the best essay describing their individual experience of living with their condition. Stine Björk Brondum Jefsen, Aarhus, Denmark, was awarded the 2021 prize for her essay 'On an equal footing'.

The EULAR President delivered the Closing Remarks, beaming with delight about the successes and collaboration exhibited by EULAR this past year: "We are proud of what EULAR had become: a global network for progression in rheumatology with as of this year an international research centre and new statues. The EULAR family is a fusion of physicians, healthcare professionals, patient [representatives] and the EULAR secretariat. Together with one goal: to improve the lives of people with rheumatic diseases." ■

"The really big breakthroughs happen when we decide to be collaborators."

EULAR 2021 REVIEWED →

"This variant leads to the overexpression of MUC5B which causes the development of pulmonary fibrosis and is the leading genetic risk factor for causing RA-ILD"

Rheumatoid Arthritis and Interstitial Lung Disease Linked by Genetic Variant

THE INFLAMMATORY autoimmune disease rheumatoid arthritis (RA) causes pain, swelling, and stiffness in the joints. RA inflammation also affects other body systems and can lead to fatigue. Interstitial lung disease (ILD) affects up to 10% of patients diagnosed with RA and is one of the main causes of death in these patients. A cohort study involving a biomedical database of 250,000 individuals in Finland, presented at EULAR 2021 showed that people with a *MUC5B* gene variant have a substantial lifetime risk of ILD, which in turn leads to an increase in morbidity. These collected data are significant and could assist healthcare professionals in identifying patients diagnosed with RA with a high chance of developing ILD.

The *MUC5B* gene regulates the protein mucin, which play an important role in the body's natural defence of infection. The promoter variant called rs35705950 is a variant of the *MUC5B* gene and has an allele frequency of 0.1 in the Finnish population; this variant leads to overexpression of *MUC5B,* which causes the development of pulmonary fibrosis and is the leading genetic risk factor for RA-ILD. Antti Palomäki and team utilised the FinnGen biobank samples, which contain up to 46 years of follow-up genetic data nationwide, to report the risk developing RA-ILD in patients diagnosed with RA by identifying the carriers of *MUC5B* promoter variant.

The results showed that of 248,400 people, 5,534 had been diagnosed with RA and 178 of these (3.2%) had developed RA-ILD. The *MUC5B* promoter variant was a strong biomarker, demonstrating high risk of developing ILD in patients diagnosed with RA. Of patients diagnosed with RA and carrying the *MUC5B* promoter variant, 14.5% had a lifetime risk at age 80 of developing ILD, compared with 5.2% of non-carriers. Additionally, in the general population of people without RA, *MUC5B* promoter carriers and non-carriers had risks of developing ILD of 3.9% and 1.3%, respectively. The researchers found that the risk variance became apparent at the age of 65. Male patients diagnosed with RA and carriers of *MUC5B* promoter variant were the highest-risk group, with 18.5% risk of developing ILD compared with 8.5% of non-carriers. ■

Study Suggests No Link to Increased Risk of Serious Infections with New Disease-Modifying Anti-rheumatic Drugs

RHEUMATOID arthritis (RA) in elderly patients is mainly associated with significant risk of serious infections. Certain anti-rheumatic treatments have been linked to higher risk of infections compared to others; however, the degree of these links is yet to be decided. A prospective, observational cohort study, carried out in Germany and presented at EULAR 2021, addressed the connection between a new class of anti-rheumatic drugs and its association with higher infection rates.

Biologic disease-modifying anti-rheumatic drugs (bDMARDs) and JAK inhibitors (JAKi), were the two new classes of drugs studied to assess their effects in elderly patients diagnosed with RA. The results of this Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) study were presented by Strangfeld and colleagues at the congress this year. The investigation enrolled 2,274 patients diagnosed with RA over the age of 70 years to start a new DMARD treatment following an ineffective use of a conventional synthetic treatment (csDMARD).

A total of 626 serious infections were noted in 425 of the enrolled patients. The observed data showed that serious infections were more prevalent in patients receiving csDMARDs compared to bDMARDs or JAKi; however, these data were not statistically significant, as serious infections were related to other underlying causes such as the use of glucocorticoids, increased disease activity, and other medical conditions such as diabetes, chronic pulmonary disease, and kidney disease. Increased physical capacity in the enrolled patients was linked to a decrease in the risk of serious infections. Overall, the results demonstrated that bDMARDs and JAKi treatments were not associated with increased risk of serious infection in elderly patients diagnosed with RA over 70 years old. ■

"the results demonstrated that bDMARDs and JAKi treatments were not associated with increased risk of serious infection in elderly patients diagnosed with RA over 70 years old."

Effectiveness and Safety of Faecal Microbiota Transplantation for Active Peripheral Psoriatic Arthritis

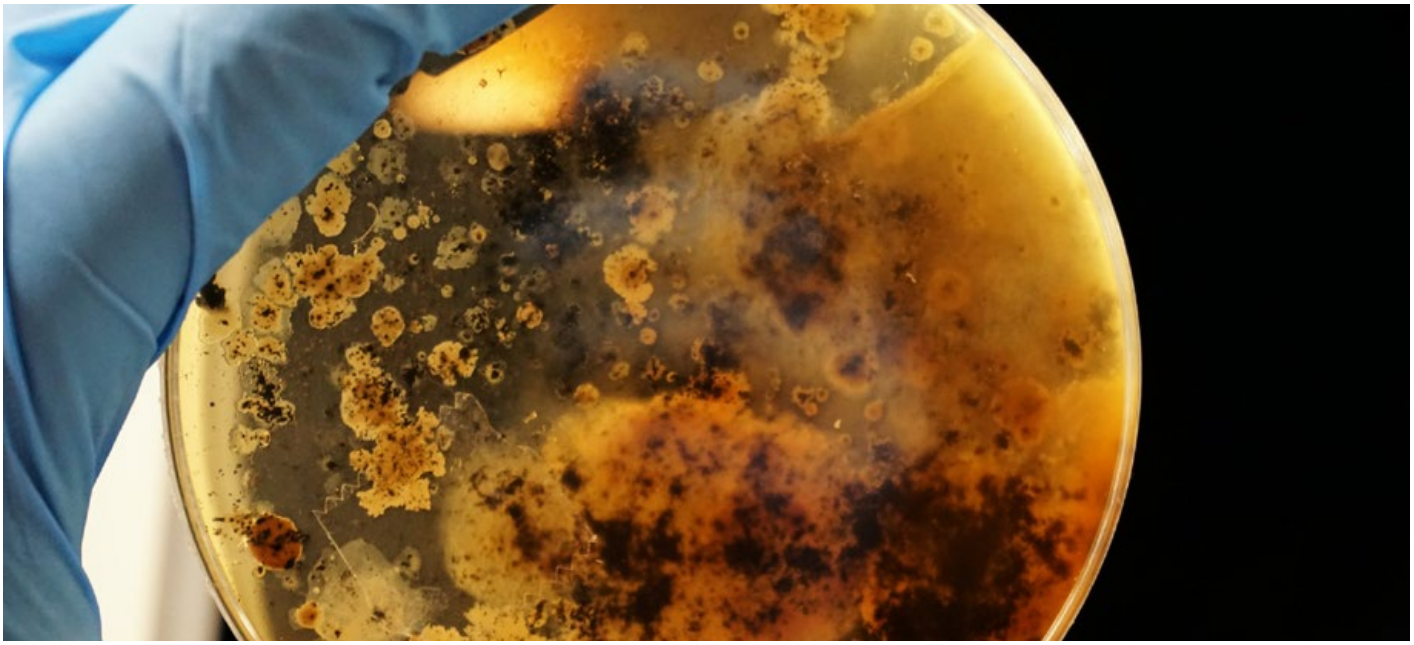
TARGETING gut dysbiosis and restoring microbiome homeostasis through the use of faecal microbiota transplantation (FMT) has been suggested as a novel therapeutic strategy for the management of extraintestinal inflammatory disorders; however, causality remains to be established. For this reason, Maja Skov Kragsnaes, Department of Rheumatology, Odense University Hospital, Denmark, and colleagues conducted a double-blind, parallel-group, sham-controlled superiority trial to evaluate the efficacy and safety of FMT in psoriatic arthritis (PsA), and shared their findings at EULAR 2021.

"Overall, the research findings clearly illustrate that FMT was inferior to sham in treating immune-mediated active peripheral PsA."

In this proof-of-concept study, 31 adult patients with active peripheral PsA (defined as ≥3 swollen joints) were randomly assigned, despite ongoing treatment with methotrexate, to receive either gastroscopic-guided FMT or sham transplantation into the duodenum. The transplants (50 g faeces) came from one of four healthy, thoroughly screened, anonymous stool donors. The primary end-point was the proportion of patients experiencing treatment failure (e.g., requiring treatment intensification) during the 26-week trial period. The first key secondary end-point was change in Health Assessment Questionnaire Disability Index (HAQ-DI) score from baseline to Week 26. Safety was also monitored throughout the trial.

Treatment failure occurred more frequently in the FMT group than in the sham group (60% versus 19%, respectively; risk ratio: 3.20; 95% confidence interval: 1.06–9.62; p=0.018). Similarly, during the course of the entire observation period the rate of treatment failure was statistically significantly higher in the FMT group compared with the sham group. Improvement in HAQ-DI score also differed between groups (0.07 and 0.30 for FMT and sham, respectively; p=0.031). Neither FMT nor sham appeared to result in serious adverse events.

Overall, the research findings illustrate that FMT was inferior to sham in treating immune-mediated active peripheral PsA. ■



"...analysis confirmed the significant relationship between TNFi use for 12 or more months in the previous interval and progression of the sacroiliitis sum score"

Tumour Necrosis Factor Inhibitors and Disease Progression in Patients with Spondyloarthritis

SACROILIITIS, characterised by inflammation of the sacroiliac joints, is a primary manifestation of axial spondyloarthritis (axSpA). Observational cohort studies have revealed that there is a low but detectable level of radiographic sacroiliitis progression, which may impact the function of patients with axSpA. Recent data showed that a longer duration of tumour necrosis factor inhibitor (TNFi) treatment delays spinal progression in axSpA; however, there is no clear consensus regarding the effect of TNFi usage on radiographic progression in sacroiliac joints. Therefore, Murat Torgutalp, Division of Gastroenterology, Infectious Diseases and Rheumatology, Charité – Universitätsmedizin Berlin, Germany, and colleagues investigated the longitudinal association between the progression of radiographic sacroiliitis and TNFi therapy in patients with early axSpA, sharing their findings at EULAR 2021.

In total, 301 patients (166 with non-radiographic axSpA and 135 with radiographic axSpA) from the German Spondyloarthritis Inception Cohort (GESPIC) were included in the analysis. Two trained central readers scored the radiographs according to modified New York criteria. If both scored an image as definitive radiographic sacroiliitis, the patient was classified as having radiographic axSpA; the mean of both readers was used to calculate the sacroiliac sum score. Analysis focused on the association between TNFi use (previous and current) and radiographic sacroiliitis progression, defined as the change in sacroiliitis sum score over 2 years.

At baseline, 3% of patients (n=9) were treated with a TNFi and 28.9% of patients (n=87) received at least one TNFi during the entire follow-up period. Receiving ≥12 months of TNFi in the previous interval was associated with a lower progression of the sacroiliitis sum score compared to not receiving TNFi in the previous interval. This was not recorded in patients who received TNFi for longer than 12 months in the 2-year interval. Adjusted multivariable longitudinal generalised estimating equations analysis confirmed the significant relationship between TNFi use for 12 or more months in the previous interval and progression of the sacroiliitis sum score.

In conclusion, TNFi therapy was associated with slowing of the progression of radiographic sacroiliitis in patients with axSpA. This effect became apparent 2–4 years after initiation of the treatment. ■

A EULAR Framework and Task Force for Gender Equity

GENDER equity was one of the topics centre stage at EULAR 2021, with the congress announcing its plans to accelerate gender-equitable career advancement in academic rheumatology through a framework and task force.

The EULAR Task Force on Gender Equity in Academic Rheumatology set out to establish how much of an unmet need there is for supporting female rheumatologists, healthcare professionals, and non-clinical scientists in academic rheumatology. Once understanding the extent of the unmet need, the objective was to develop a framework and address the demand through EULAR and Emerging EULAR Network (EMEUNET).

EULAR collected possible interventions to accelerate gender-equitable career advancement in academic rheumatology through the following actions: expert opinion from the multi-disciplinary Task Force was acquired, survey data from EULAR scientific member society leaders were analysed, a narrative review of the relevant literature was studied, and EULAR, EMEUNET, and EULAR Executive Committee members were consulted. The interventions were subsequently ranked from 1 to 5 by Task Force members in order of perceived priority: 1 = very low; 5 = very high.

A framework containing 29 possible interventions was composed and covered six thematic areas: 1) EULAR policies; 2) advocacy and communication; 3) the EULAR congress and the associated symposia; 4) training courses; 5) peer/mentoring support; and 6) EULAR funding. The framework that was formulated gives structured interventions for advancing gender-equitable career progression in the field of academic rheumatology. ■

"The framework that was formulated gives structured interventions for advancing gender-equitable career progression in the field of academic rheumatology."

"The study showed that in a group of patients with rheumatic diseases, the spread of SARS-CoV-2 infection is greater than what has been previously observed through swab diagnosis."

True COVID-19 Spread and Prevalence is Greater than Currently Observed

TRUE prevalence and spread of COVID-19 is much greater than what is being recorded, because current statistics are only based on swab-diagnosed COVID-19 cases. Data shared at EULAR 2021 from Lombardy, Italy, reported that the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is still unknown and is much greater than observed because of the high proportion of subclinical infection, but is consistent with a healthy population.

The data were published as part of the EULAR 2021 poster presentations and are part of the MAINSTREAM project, a seroprevalence cross-sectional study performed by Ennio Giulio Favalli, Gaetano Pini Institute, Milan, Italy, and colleagues between 4th May and 16th June 2020 to evaluate the prevalence of anti-SARS-CoV-2 antibodies in a large cohort of patients with rheumatoid arthritis or spondylarthritis. Individuals in the study cohort were being treated with biological or targeted synthetic disease-modifying anti-rheumatic drugs and lived in Lombardy, a COVID-19 high-endemic area of Italy. Individuals (n=300) were tested for IgA, IgG, and IgM antibodies against three viral antigens: the receptor-binding domain, nucleoprotein, and spike protein. The data were then compared to the region's healthy population. The participants completed a questionnaire regarding the symptoms consistent with COVID-19, comorbidities, and risk factors.

In total, 65% of the participants had rheumatoid arthritis, 23% had psoriatic arthritis, and 21% had ankylosing spondylitis. The main therapy used for treatment were TNF inhibitors (57%), followed by abatacept (20%), IL-6 (11%), and JAK inhibitors (5%). Four out of the 300 individuals had been previously diagnosed with COVID-19 by a nasopharyngeal swab test.

On evaluation of Ig titres, 13.3%, 9%, and 13.6% of patients were positive for IgA, IgG, and IgM, respectively, and there was no significant difference when compared to the healthy population. Fifty-five percent of the patients who were seropositive were asymptomatic, 19.6% had major symptoms, 16% had minor symptoms, and 7% were hospitalised, however, no intensive care unit admissions or deaths were recorded. The titres of IgA, IgG, and IgM to the virus receptor-binding domain were higher in patients with both major and minor symptoms, compared to patients who were asymptomatic. In regard to age, sex, rheumatic diagnosis, and treatment, no differences were found between seronegative and seropositive patients.

The study showed that in a group of patients with rheumatic diseases, the spread of SARS-CoV-2 infection is greater than what has been previously observed through swab diagnosis. The rheumatic diseases and the ongoing therapies did not appear to have any impact on antibody positivity. ■

Uveitis Drug Withdrawal Studied in Children with Arthritis

EMERGING evidence during EULAR 2021 has highlighted risk of uveitis in patients being treated for juvenile idiopathic arthritis (JIA), specifically upon withdrawal of disease-modifying anti-rheumatic drugs (DMARD). This complication can have serious, lasting implications upon vision, leading to blindness if uncontrolled, and occurs frequently as a stand-alone condition in close to 20% of children with JIA.

EULAR 2021 gave the opportunity to Jens Klotsche and his colleagues to share an alarming risk profile they identified, involving children discontinued from DMARDs in extended oligoarthritis and rheumatoid factor-negative polyarthritis categories of JIA. The German Biologics in Pediatric Rheumatology (BiKeR) registry and Juvenile arthritis Methotrexate/Biologics long-term Observation (JuMBO) study provided data for analysis, presenting 2,041 children and stating adverse uveitis events during treatment and after removal of DMARDs.

Etanercept was taken in just over half (58%) of the children included, alongside 635 patients using methotrexate monotherapy (31%) and adalimumab (10%). Critical findings demonstrated children with uveitis had a lower age at JIA onset in comparison to patients without. Recurrent uveitis events were reported in 93 children, to a total of 142 events; for 27 of these children it was an incident reported during follow-up, 19 of which were flare-ups after the age of 18.

In the first 24 months after discontinuation, uveitis events were significantly more frequent, and in the first 3 months after DMARD removal. A notable finding was that children with a methotrexate dose of ≤10 mg/m^2 had a higher likelihood for uveitis events. The study Findings that uveitis relapses are common, and patients who stop DMARDs are at risk, are expected to promote regular uveitis screening after treatment is withdrawn. Sharing these findings at EULAR 2021 will help raise awareness among rheumatologists and ophthalmologists, in an event aiming to improve treatment, prevention and rehabilitation of rheumatic and muskuloskeletal diseases. However, it should be acknowledged this is the first prospective study to look at this relationship. ■

"Findings that uveitis relapses are common, and patients who stop DMARDs are at risk, are expected to promote regular uveitis screening after treatment is withdrawn."

Air Pollution and Passive Smoking Linked to Arthritis

ANALYSES of increasing evidence of associations between air pollution, passive exposure to smoking, and risk of developing rheumatoid arthritis (RA) were shared at EULAR 2021. Based on a large female population in France, the first study's findings offered insight into how future initiatives might combat the widespread influence of RA. Previous literature has shown active smoking to be the most reproducible risk factor for RA. A second study in Italy investigated air pollution levels that exhibit associations with failure of biologic therapy.

During EULAR 2021, Nguyen and colleagues explained their selection of a large prospective cohort of healthy females in their French study, examining 79,806 profiles, of which 698 cases of RA were identified. Looking at the whole population, 13.5% were exposed to passive smoking as children, 53.6% as adults, and 8.25% to both. They drew the conclusion that passive smoking in childhood and adulthood was positively associated with risk of RA, particularly among female patients who had never smoked themselves. These results suggest smoking by-products, via either active or passive inhalation, could generate autoimmunity towards antigens involved in RA pathogenesis. It should be considered that the conclusions drawn are limited to a female population, but future directives will build on the findings of the current study, given that RA is more common in female than male patients.

"Authors concluded environmental air pollution a determinant of poor response to biologic treatment, based on their findings future action should decrease fossil fuel emissions to benefit the persistence rate of therapies."

EULAR 2021 discussion progressed to a study by Adami and colleagues, investigating links between the lungs and inflammatory arthritis. To examine the association between concentration of air pollutants and biologic drug retention rates in people with chronic inflammatory arthritis, they conducted a case cross-over study involving 1,286 patients in Verona, Italy.

Of the cohort, 1,286 had chronic inflammatory arthritis, and the authors found an exposure-dependent relationship between air pollutants and markers of inflammation in patients of this sub-category. At the European Union's health protection limit for pollution (30 µg/m^3) there was a 38% higher risk of having altered C-factory smoke reactive protein levels. The authors concluded that environmental air pollution was a determinant of poor response to biologic treatment; based on their findings, future action should decrease fossil fuel emissions to benefit the persistence rate of therapies. ■

Increased Risk of COVID-19 in Inflammatory Joint Disease

AT EULAR 2021, population-based data shared by Vivekanantham and Bower examined the association between rheumatoid arthritis (RA) and diagnosis, hospitalisation, and death related to COVID-19. Amidst the pandemic, the findings were of great interest to people with inflammatory diseases, who may have higher risk of severe outcomes with the virus. Results from Spain suggest individuals with RA have increased risk of COVID-19 diagnosis and hospitalisation compared to the general population, while a database in Sweden found that the risk of severe infection was increased amongst patients with inflammatory joint diseases.

The first studied section included 80% of the population of Catalonia, with information linked to regional hospital figures between March and May 2020, to a total of 5,586,565 participants. Of this population, 16,344 had RA and exhibited a positive association with COVID-19 diagnosis and hospitalisation. It should be acknowledged that in this Spanish study the authors did not find any association between RA and worsening diagnosis to hospitalisation, or hospitalisation to death. Future studies will address factors linking RA and COVID-19, including comorbidities, underlying RA activity, and immunosuppressive medications.

The Swedish database studied mortality and risk of severe COVID-19 in 110,567 people with varying chronic inflammatory joint diseases, comparing this subset with 484,277 of the general population. Analysing admissions to hospital and deaths, the absolute risk of death from any cause in 2020 was observed to peak in mid-April. This peak was higher than that of 2015-2019, but the relative risk of death against the general population remained similar. In those with inflammatory joint disease, Bower shared that risk of hospitalisation, admission to intensive care, and death due to COVID-19 was 0.3%, 0.03%, and 0.07% respectively.

The studies discussed at EULAR 2021 bring forward crucial findings that may prove useful foundations for investigating the complex relationship between inflammation and infectious disease, specifically COVID-19. ■

"Results from Spain suggest individuals with RA have increased risk of COVID-19 diagnosis and hospitalisation compared to the general population, while a database in Sweden found that the risks of severe infection was increased amongst patients with inflammatory joint diseases."

Managing Chronic Pain in Osteoarthritis and Rheumatoid Arthritis

Theo Wolf
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ON DAY 3 of the European Alliance of Associations for Rheumatology (EULAR) 2021 Congress, participants from across the globe accessed the virtual platform to join Jon Lampa, Associate Professor, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden, and his panel as they explored the challenges and opportunities of managing chronic pain in osteoarthritis and rheumatoid arthritis.

OSTEOARTHRITIS PAIN AND MECHANISM-BASED TREATMENTS

Malvika Gulati, Rheumatology Registrar, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, UK, began by discussing the management of chronic pain in hand osteoarthritis.

While not required for a diagnosis, blood tests are recommended to exclude alternative causes, such as rheumatoid arthritis or gout. According to Gulati, hand X-rays are often performed to help differentiate hand osteoarthritis from conditions with similar features, including psoriatic arthritis. Common findings from radiographic imaging include loss of joint space, osteophytes, and subchondral sclerosis.

Gulati explained that no single test on its own can be used to define hand osteoarthritis (likelihood ratio <10); however, a composite of features substantially enhances the probability of diagnosis. The chance of a person having hand osteoarthritis when Heberden's nodes alone were present was 20%; however, this increased to 88% when coupled with an age over 40 years, a positive family history of nodes, and supportive X-ray features (joint space narrowing in any finger joint).

Pharmacological therapies are frequently administered to individuals with hand osteoarthritis; however, there are numerous other management strategies that could be used, as outlined by Gulati. Education and training in ergonomic principles, the pacing of activities, and the use of assistive devices should be offered to all patients. Moreover, hand exercises can have beneficial effects on pain, function, stiffness, and grip strength. Gulati stressed that patients should be advised to continue with exercises and not view these as a one-off intervention. Orthoses should also be considered for symptom relief in people with thumb-base osteoarthritis. Although a number of patients have reported finding heat helpful, the evidence for a possible beneficial effect is weak and conflicting. With respect to pharmacotherapy, Gulati noted that there is

"Education and training in ergonomic principles, the pacing of activities, and the use of assistive devices should be offered to all patients"

good evidence to support the use of topical anti-inflammatories, which are well-tolerated and have a much better side effect profile compared to oral anti-inflammatories. It is recommended that oral analgesics are considered for a limited duration and at the lowest dose possible. There is some evidence for the superiority of chondroitin over placebo for pain and function. Therefore, if patients are keen to take this, they may do so. Trials investigating conventional and biologic disease-modifying anti-rheumatic drugs (e.g., hydroxychloroquine and anti-IL-1) have demonstrated a lack of efficacy. Finally, Gulati mentioned the HOPE study in the Netherlands, in which 10 mg prednisolone was administered for 6 weeks to individuals with inflammatory features of hand osteoarthritis on ultrasound. Although benefit was seen without an excess of adverse events, 10 mg of oral prednisolone is not an insignificant dose. Consequently, Gulati emphasised that glucocorticoids should not be prescribed for prolonged periods of time. Surgery is an option for individuals who have tried the above therapies but continue to be symptomatic. A trapeziectomy should be considered in people with thumb-base osteoarthritis, and arthrodesis or arthroplasty in people with interphalangeal osteoarthritis.

Gulati provided an overview of recent American College of Rheumatology (ACR) recommendations, which advocate the use of cognitive behavioural therapy and centrally acting drugs (e.g., duloxetine). Intra-articular hyaluronic acid is conditionally advised against because studies with a low risk of bias showed no treatment effect.

To summarise, Gulati reiterated the importance of education and exercise, and stressed that treatment must be multidisciplinary and multimodal, rather than solely focused on drugs.

"patients who respond well to advanced immunotherapies for the control of peripheral inflammation often continue to report clinically significant levels of pain"

CHRONIC PAIN IN RHEUMATOID ARTHRITIS AND STRATIFIED TREATMENT APPROACHES

Neil Basu, Senior Clinical Lecturer of Rheumatology, University of Glasgow, UK, discussed the importance of stratified targeted treatment strategies for chronic pain in rheumatoid arthritis.

Basu started by explaining that patients who respond well to advanced immunotherapies for the control of peripheral inflammation often continue to report clinically significant levels of pain, with one study showing that a substantial proportion of individuals with complete remission still had a Short Form 36 (SF-36) score of <40. The disconnect between improvements in the degree of inflammation and improvements in the severity of symptoms suggests that there is contribution from additional pain mechanisms that are distinct from peripheral inflammation. Central sensitisation, the primary underlying cause of chronic pain in fibromyalgia, may represent one such pathway, Basu highlighted.

This is supported by epidemiological data, which found that fibromyalgia has a prevalence of 13–25% in people with rheumatoid arthritis versus 1–5% in the general population. From a biological perspective, quantitative sensory testing also lends credence to central sensitisation. Individuals with rheumatoid arthritis and higher 'fibromyalgianess' were found to have a decreased pain threshold around the tibia and other non-articulated surfaces.

Next, Basu explained that the co-existing central pain mechanism artificially inflates commonly used measures of peripheral inflammatory pain. For example, one study found that individuals with concomitant fibromyalgia had a significantly higher disease activity score (DAS) relative to people with rheumatoid arthritis alone (5.36 and 4.03, respectively; $p<0.001$). Since many countries use the DAS score to sanction the administration of anti-inflammatory therapies, Basu revealed that inappropriate prescribing of biological treatments for pain that is not truly inflammatory in origin typically occurs. Indeed, research from Denmark highlighted that 64% of people with co-existing fibromyalgia and rheumatoid arthritis received biologics relative to 32% of individuals with rheumatoid arthritis alone.

Basu therefore suggested that EULAR evidence-based guidelines for primary fibromyalgia should be translated to people with co-existing central pain mechanisms and rheumatoid arthritis. The focus is around education and physical therapy. However, for patients who have not responded to either of these strategies, the guidelines indicate a stratified approach. This includes the use of psychological therapies for people with concomitant depression, pharmacotherapy for patients with severe pain and sleep disturbance, and multimodal rehabilitation programmes for individuals who do not do well despite these interventions. With regard to pharmacological treatments, Basu stated that duloxetine has been recommended for the treatment of chronic pain, particularly more central pain mechanisms. A recent study conducted in Japan revealed that this drug provided benefit in people who had achieved remission of rheumatoid arthritis but still suffered pain. Furthermore, an evaluation of various immunotherapies illustrated that JAK inhibitors (e.g., baricitinib) demonstrated a superior analgesic effect relative to the gold standard of anti-TNFα agents. Basu hypothesised that this difference could be explained by the fact JAK inhibitors are better at inhibiting cytokines such as granulocyte-macrophage colony-stimulating factor, which are known to be important in pain pathways.

To conclude, Basu discussed the assessment of pain in people with rheumatoid arthritis. If there is no evidence of inflammation, it is feasible to persevere with existing immunotherapy, focus on other dimensions, such as structural damage, and look beyond the joints, since pain mechanisms may be centrally driven rather than around the periphery. ■

Artificial Intelligence in Rheumatic Diseases: Can It Solve the Treatment Management Puzzle?

This symposium took place on 4th June 2021, as part of the European Alliance of Associations for Rheumatology (EULAR) 2021 virtual congress

Chairperson: Ernest Choy[1]

Speakers: Ignacio Medrano,[2] Ernest Choy,[1] Laure Gossec[3]

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2. Savana, Madrid, Spain
3. Sorbonne Université and Pitié-Salpêtrière Hospital, Paris, France

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Meeting Summary

Artificial intelligence (AI) describes the use of technology to mimic the cognitive functions of a human being, such as intelligent behaviour and critical thinking. AI-based technologies are already being used across healthcare settings for applications such as image analysis and diagnosis; nevertheless, the full potential of AI to guide disease management in rheumatology has yet to be realised.

Rheumatoid arthritis (RA) is a chronic inflammatory disease with a heterogeneous clinical presentation and pathogenesis. Early intervention with disease-modifying therapies can alter the course of the disease, preventing irreversible joint damage and improving long-term outcomes. However, barriers to early diagnosis of rheumatic diseases mean that many patients receive delayed treatment, leading to sub-optimal long-term outcomes. Patients at high risk of disease progression are particularly suitable for early intervention, although accurately identifying these patients can be challenging. AI approaches to aid in early diagnosis and prediction of disease progression are emerging in rheumatic diseases, but these have yet to enter clinical practice.

Prediction of response to treatments such as anti-TNFs is another area where AI could play an important role in the future. Many patients with rheumatic diseases have a sub-optimal response or loss of response to certain therapies, and methods to predict response are lacking. AI approaches for predicting treatment response are under investigation in rheumatology, and many potential biological predictors of response to anti-TNFs have been identified. However, these studies are still at an exploratory stage, and the results will need validation before they can be implemented in clinical practice.

AI approaches have the potential to transform the treatment of rheumatic diseases, from advancing early diagnosis to facilitating a more individualised treatment approach, with the overall aim of improving patient outcomes.

Introduction

This symposium was developed to consider the future role that AI might play in the management of rheumatic diseases. First, Ignacio Medrano considered the current use of AI in healthcare and its possible future applications. Ernest Choy subsequently discussed the potential role of AI in facilitating early intervention in rheumatic diseases. Finally, Laure Gossec outlined opportunities to use AI in the prediction of treatment response and considered the ethical and practical implications of using AI to analyse 'Big Data'.

Artificial Intelligence: The Future of Medicine?

AI is a term used to describe the use of computers and other technology to simulate intelligent behaviour and critical thinking that mimic the cognitive functions of a human being.[1] Research into the application of AI techniques in medicine has been ongoing for several decades; in 2016, most AI investment went into research in the healthcare sector.[1] The potential applications of AI in medicine are vast and, ultimately, are likely to have significant impact on patient care and clinical decision-making in rheumatology.[2]

There are potential applications for AI-based technologies in almost every aspect of modern life. One well-known example of AI is the programme Google Translate (Google, Mountain View, California, USA), which can automatically translate text to and from a multitude of languages. Google Translate uses an algorithm based on machine learning, an AI technique, which is programmed to learn from a set of solved problems. This approach removes the need for any understanding of grammar or syntax and allows the algorithm to infer the rules of any language and apply them to solve unseen problems.

AI-based technologies are emerging within healthcare settings, but more research is needed before the full potential of AI is realised across a wide range of clinical applications. Automated analysis of medical imaging is one area where AI may have particular value because manual analysis of these images is resource intensive and can be subject to inter-observer variability.[3] In 2016, a deep-learning algorithm was developed that detected diabetic retinopathy and macular oedema in retinal fundus images with a high degree of specificity and sensitivity.[4] Based on these findings, in 2018 the U.S. Food and Drug Administration (FDA) permitted marketing of the first AI-based medical device that could be used in a primary care physician's office to detect cases of diabetic retinopathy.[5] AI techniques also have the ability to extract unexpected patterns and associations from medical images. For example, a deep-learning algorithm has been developed that can predict cardiovascular risk factors (such as age, sex, and systolic blood pressure) from retinal fundus images.[6] Previously, it had not been considered that these factors could be identified from retinal images.[6] This demonstrates the power of AI techniques to go beyond human interpretation to see associations between multiple variables that the human brain cannot detect.

Other applications of AI in medicine have been investigated, including the use of laboratory data, medical records, and molecular biology outputs to aid in diagnosis, treatment selection, and

prediction of prognosis. For example, a model based on demographic and laboratory data was developed to predict treatment non-response in patients with Crohn's disease.[7] AI systems have also been used to assist selection of an appropriate antibiotic prescription.[8] Numerous AI-based technologies have been approved by the FDA across fields including oncology, cardiology, and emergency medicine.[9]

The use of AI in rheumatology is not as advanced as in other therapy areas; more research is needed into the development and implementation of AI techniques to aid with diagnosis and management of rheumatic diseases. However, some promising research has been undertaken in arthritis; in particular, a study that aimed to detect early osteoarthritis by examining pre-symptomatic cartilage texture maps from MRI using an automated pattern-learning system.[10] Future applications of AI in rheumatology could include examining associations between genotype and phenotype, as well as using AI to extract and analyse clinical data from electronic health records (EHR). EHRs contain large amounts of real-world patient data in both a structured form (information such as International Classification of Disease [ICD] codes), as well as in a free-text arrangement (e.g., the narrative from the healthcare provider notes).[11] It can be challenging to identify or classify patients with certain conditions using structured information alone because their use can vary substantially across healthcare systems. This is a particular issue when trying to identify patients with axial spondyloarthritis (axSpA) from EHRs because the evolving disease concept means there has historically been a lack of specific ICD codes. To overcome this issue, a technique called natural language processing was used in one study to extract key disease concepts from free-text data in EHRs.[11] These data were then combined with structured ICD code data to develop algorithms designed to identify patients with a high probability of having axSpA. When identifying patients with axSpA, the algorithms that incorporated free-text data outperformed the algorithms that used ICD codes alone.[11] Algorithms incorporating data derived from natural language processing expand the amount of EHR data that can be analysed and offer exciting opportunities for clinical research in the future.

AI in healthcare is a rapidly evolving field, but it is important to proceed cautiously and responsibly. In a recent proof-of-concept study, a deep-learning algorithm was used to detect patients with atrial fibrillation based on facial video images.[12] The researchers used the approach to identify patients with atrial fibrillation with a high degree of accuracy and could facilitate high-throughput screening in settings such as hospital waiting rooms.[12] However, the non-contact nature of this type of examination raises important questions and concerns about patient consent, privacy, and confidentiality.[13] As technology advances, regulation will be required to ensure that tools are used appropriately and ethically.

Can Artificial Intelligence Find the Missing Pieces Needed to Facilitate Early Intervention?

RA is a chronic inflammatory disease mainly affecting the joints but is heterogeneous in terms of clinical presentation and disease pathogenesis.[14] Patients with RA have variable clinical courses characterised by continuously active disease or periods of relapse and remission.[15] In RA, a 'window of opportunity' is thought to exist between the onset of inflammation and the start of radiographic damage. Early intervention with disease-modifying anti-rheumatic drugs (DMARDs) during this 'window of opportunity' aims to alter the disease course before irreversible joint damage occurs, improving long-term outcomes.[15]

Early diagnosis and early intervention with effective therapies remain challenges in rheumatology. A study in patients who were newly presenting with RA or unclassified inflammatory arthritis showed delays occurring at several points in the care pathway. The median time between symptom onset and seeing a rheumatologist was 27.2 weeks, with only 20% of patients being seen within 3 months of symptom onset.[16]

Diagnostic Delay in Rheumatology

A number of potential barriers to early diagnosis in RA have been identified, including a broad differential diagnosis, heterogeneous

presentation at early stages of disease, differences in symptom onset, and the fact that no single laboratory test is specifically characteristic of RA.[16,17] Delayed diagnosis is not just a problem in RA. For patients with ankylosing spondylitis (AS) and psoriatic arthritis, an average delay of ≥8 years between symptom onset and disease diagnosis has been reported.[18] Earlier diagnosis of rheumatic diseases is needed to ensure patients begin treatment before irreversible structural damage occurs.

AI approaches to improve diagnosis are being investigated in rheumatology (Figure 1). In one study, machine learning was used to develop an algorithm to identify patients with RA from EHRs.[19] Eight diagnosis or medication codes within the EHRs were found to be associated with a diagnosis of RA and were used to build the final model. The resulting algorithm had an accuracy of 92.3% for identifying patients with RA, comparable with expert clinical knowledge-based methods.[19] In a separate study, an artificial neural network model was constructed that could classify patients as having RA, osteoarthritis, or being non-arthritic, based on differentially expressed serum cytokines. The resulting model was able to accurately diagnose 100% of test patients correctly.[20]

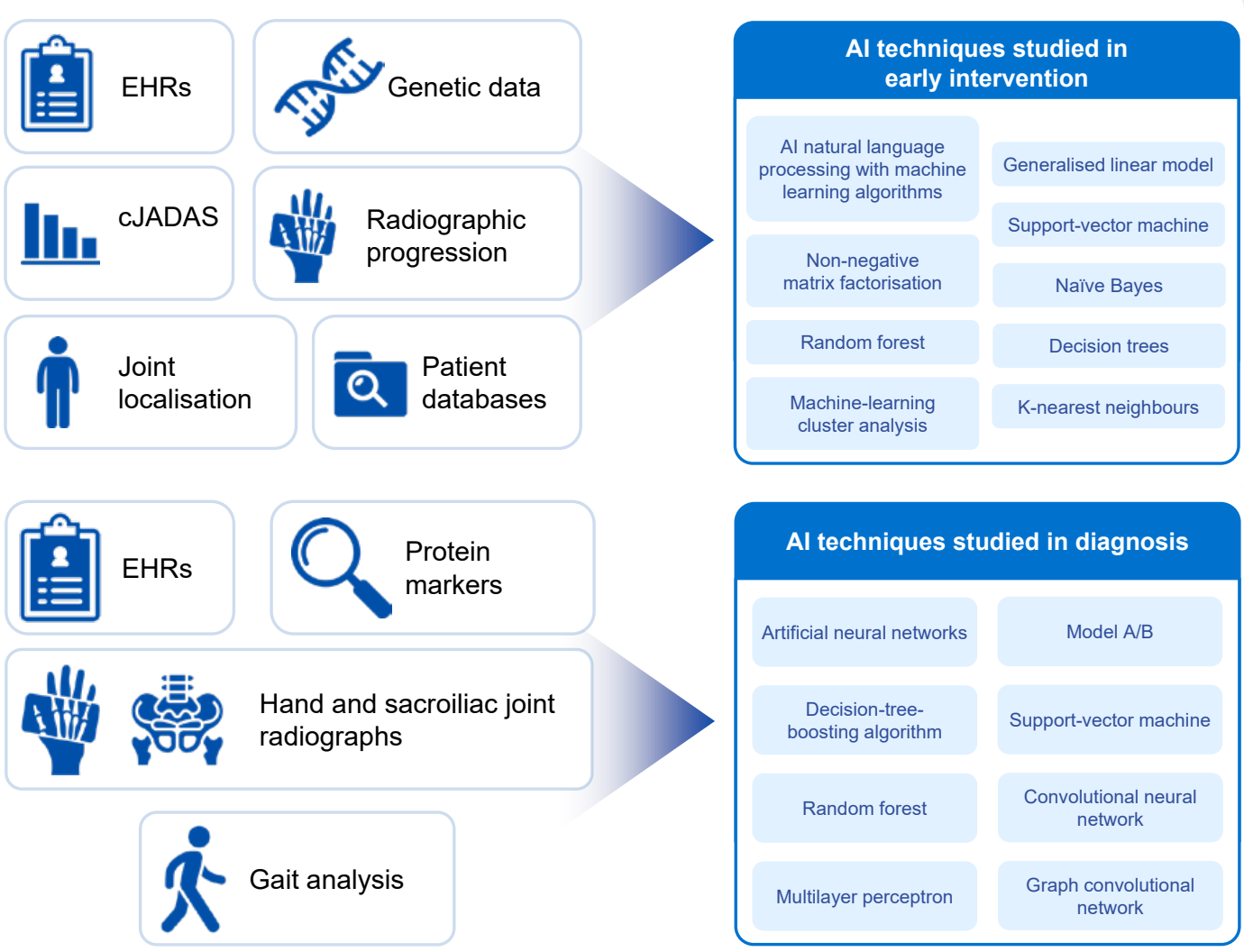

Figure 1: Artificial intelligence techniques studied in diagnosis and early intervention in rheumatic diseases.

AI: artificial intelligence; cJADAS: clinical Juvenile Arthritis Disease Activity Score; EHRs: electronic health records.

Early Intervention

European Alliance of Associations for Rheumatology (EULAR) treatment guidelines for RA recommend that in patients with an inadequate response to first-line conventional synthetic DMARDs and poor prognostic factors, a biologic DMARD or a JAK inhibitor should be added to the initial treatment strategy.[21] However, EULAR treatment recommendations are not always followed in clinical practice; a real-world study of 2,536 patients in Europe revealed that 55.4% of patients eligible to receive biologic DMARDs were not receiving them.[22]

AI approaches have been investigated to help identify patients with rheumatic diseases at high risk of progression who are particularly suitable for early intervention (Figure 1).

In patients with axSpA, machine-learning models were used to classify patients into three distinct groups based on clinical characteristics.[23] Radiographic progression was assessed over 2 years and was found to differ significantly between the three groups. As joint damage is irreversible, a model that can accurately identify patients at high risk of radiographic progression who would benefit from early aggressive treatment would be of great benefit in rheumatology.

Similarly, AI has been used to identify factors predictive of which patients with AS may require early use of anti-TNFs.[24] An artificial neural network model combined demographic and laboratory data from 595 patients with AS who were grouped according to early anti-TNF use or not. In the test data set, the model was able to predict which patients would require anti-TNF treatment within 6 months of diagnosis more accurately than conventional statistical methods. The model also identified the acute phase reactants C-reactive protein and erythrocyte sedimentation rate as important prognostic factors of early anti-TNF use.

RA is known to be heterogenous in nature from the time of diagnosis, and the molecular and cellular signatures associated with disease progression and therapeutic response are beginning to be understood.[25,26] Identification of factors that predispose a patient to a rapidly progressive disease course could inform AI models to identify patients who require early intervention.

Predicting Response to Treatment: Is Artificial Intelligence the Next Piece of the Puzzle?

AI approaches are evolving in rheumatology (Figure 2). Research has progressed from initial exploratory proof-of-concept studies, through to the development of time-saving AI-based tools, such as algorithms capable of automated image analysis. Researchers are starting to investigate algorithms to help guide clinical decisions, but we have still not reached the overall goal of AI, which is to help facilitate a fully personalised treatment approach to improve patient outcomes.

As many patients have a primary non-response, partial response, or secondary loss of response to certain treatments,[27-29] the identification of factors predictive of treatment response could help ensure patients receive the most suitable therapy to improve outcomes and avoid disease flares. AI approaches for predicting response to treatment are under investigation in patients with RA, including prediction of anti-TNF response based on integration of clinical and genetic markers, identifying anti-TNF non-responders using a biomarker panel, and predicting anti-TNF response using multiomics.[30-32]

Biomarkers for Prediction of Response

Many biomarkers already play a role in the diagnosis and management of RA,[33-35] and while a plethora of biomarkers that may predict response to anti-TNFs are currently being investigated, most are yet to be validated.

In an exploratory study in patients with RA, the ability of an AI algorithm based on a panel of biomarkers to identify anti-TNF non-responders was assessed. Machine learning was employed to generate a predictive algorithm to identify patients treated with anti-TNFs who would not achieve clinical response.[31] The algorithm was based on the top 25 features identified from a panel of gene-expression biomarkers, single-nucleotide polymorphism, and clinical data. Features were assessed in two patient cohorts prior to treatment with an anti-TNF, and clinical response was recorded. The algorithm was subsequently tested on a validation cohort and demonstrated good predictive power for identifying patients who did not respond to anti-TNF, with a positive predictive value of 89.7% and a specificity of 86.8%.[31]

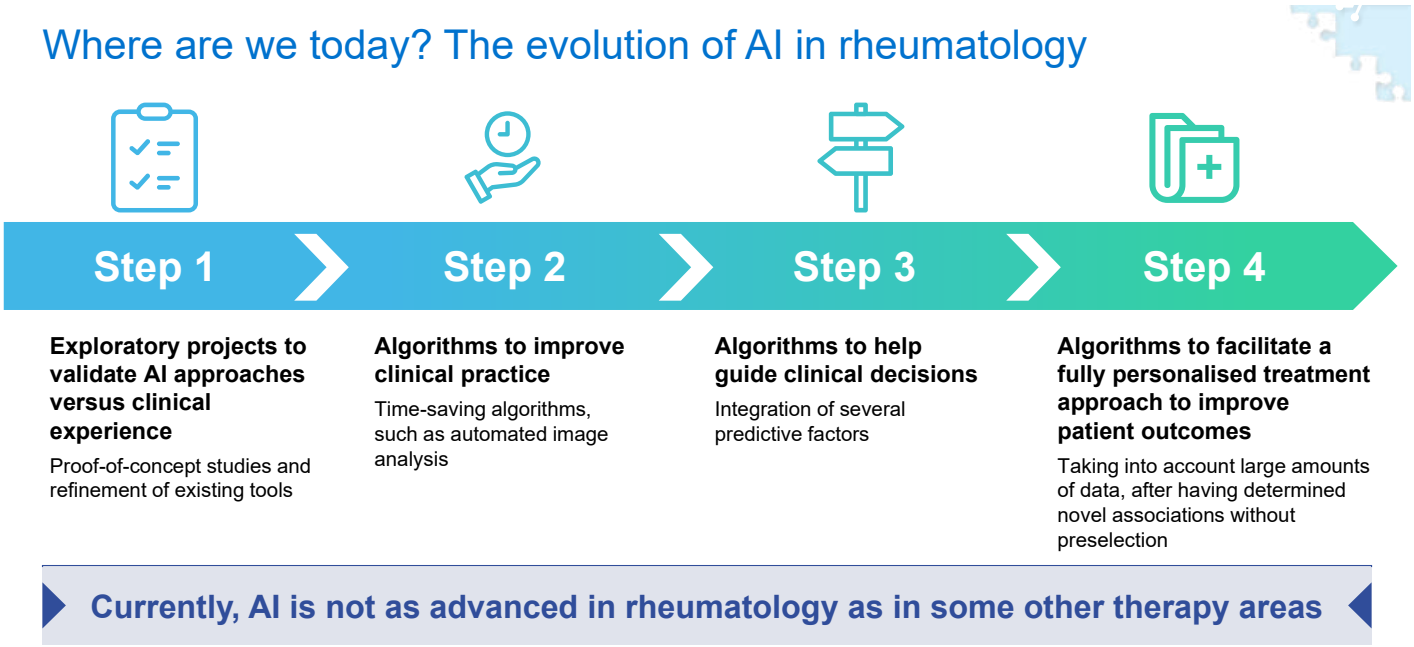

Figure 2: The evolution of artificial intelligence in rheumatology.

AI: artificial intelligence.

Electronic Health Data for Prediction of Response

In addition to the use of biomarkers, electronic health data from wearable devices also have the potential to predict response to treatment in patients with rheumatic diseases. Traditional electronic-health platforms that collect patient-reported outcomes, such as online questionnaires, place a burden on patients because they are required to actively enter information on a regular basis. Patient engagement with these platforms is known to reduce over time, especially if patients do not receive feedback on the data they enter.[36] Passive data collection, such as activity or sleep data collected using a wearable activity monitor, may be a less burdensome and more reliable way to collect data on patient wellbeing. In the ActConnect study, the potential association between physical activity assessed passively using an activity tracker and disease activity was evaluated in patients with RA or axSpA. Persistent flares in RA or axSpA were found to be associated with a lower daily step count (p=0.03).[37]

Using machine-learning techniques to analyse patient data collected from wearable devices may allow for remote monitoring of disease activity, with a high degree of accuracy and minimal burden to the patient. A pilot study of 155 patients used machine learning to assess the association between patient-reported flares and steps per minute measured using an activity tracker over a period of 3 months. A total of 224,952 hours of physical activity assessments were analysed during the study and the model accurately predicted disease flare with a sensitivity of 95.7% and specificity of 96.7%.[38] Out of 4,030 weekly flare assessments, 880 patient-reported flares were predicted by machine learning, compared with only 40 patient-reported flares that were not predicted by machine learning.[38] In the future, the use of AI to monitor disease activity may offer the potential for treatment optimisation before disease flare occurs.

These studies demonstrate the promising impact of AI in rheumatology; however, more research is needed to realise the ultimate aim of using AI to offer a fully personalised treatment approach to improve patient outcomes.

EULAR and Big Data: overarching principles

Definitions: The term 'Big Data' refers to extremely large data sets that may be complex, multidimensional, unstructured, and from heterogeneous sources, and which accumulate rapidly. Computational technologies, including AI (e.g., machine learning), are often applied to Big Data. Big Data may arise from multiple data sources including clinical, biological, social, and environmental data sources.

A For all Big Data use, ethical issues related to privacy, confidentiality, identity, and transparency are key principles to consider

B Big Data provides unprecedented opportunities to deliver transformative discoveries in RMD research and practice

C The ultimate goal of using Big Data in RMDs is to improve the health, lives, and care of people, including health promotion and assessment, prevention, diagnosis, treatment, and monitoring of disease

Figure 3: EULAR points to consider for the use of Big Data in rheumatology.[2]

AI: artificial intelligence; EULAR: European Alliance of Associations for Rheumatology; RMD: rheumatic and musculoskeletal disease.

Ethical Considerations for the Use of Artificial Intelligence and Big Data

In 2020, EULAR provided guidance on the collection, analysis, and use of extremely large datasets (known as Big Data) that may be analysed using AI in rheumatology (Figure 3).[2] EULAR recognises that Big Data provides unprecedented opportunities to transform rheumatological research and practice, with the principal aim of improving patient outcomes. However, there are multiple challenges associated with the use of Big Data in rheumatology, including issues related to privacy, confidentiality, identity, and transparency.[39]

During collection and storage of Big Data, ethics, heterogeneity of data, and data access need to be considered. EULAR has recommended that General Data Protection Regulations (GDPR) are adhered to in the European Union (EU), data are standardised, and that open data platforms are used to combat data heterogeneity and subsequent access.[39] During analysis and interpretation of Big Data, EULAR has recommended multi-disciplinary learning and collaboration to ensure that methods are compared and validated while expertise and experience grow within the field of rheumatology.[2]

Concluding Remarks

The potential applications of AI in healthcare are vast. In rheumatology, AI has the potential to facilitate earlier diagnosis and treatment and predict individual patient response to specific therapies. This move towards precision medicine could revolutionise patient outcomes, with patients receiving individualised treatment early in the disease course, thus minimising or even preventing irreversible inflammatory damage.

Despite this huge potential, AI is in its infancy in rheumatology. Preliminary data suggest that clinical, radiographic, and biologic measures may allow rheumatologists to stratify patients according to risk of disease progression. Similarly, many potential biomarkers predictive of treatment response have been identified, but they are yet to be validated. Further studies are required to refine and validate AI approaches before they can be used to guide the management of rheumatic diseases in the clinic.

In the future, it is likely that AI will help to facilitate an individualised treatment approach in rheumatology to allow optimal disease management and patient outcomes.

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Mind the Gap: Balancing Remission and Risk of Relapse in ANCA-Associated Vasculitis

This symposium took place on the 3rd June 2021 as part of the European Alliance of Associations for Rheumatology (EULAR) virtual congress

Speakers: Peter Lamprecht (Chair),[1] Neil Basu,[2] Aladdin J Mohammad[3,4]

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Meeting Summary

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an umbrella term for a group of rare, multisystem autoimmune disorders characterised by inflammation and damage to small blood vessels throughout the body.[1,2] Management is centred on immunosuppressive/immunomodulatory approaches, with glucocorticoids (GCs) providing a key cornerstone of treatment.[3] However, a clear gap exists between current clinical practice and treatment guidelines in the management of AAV, which can adversely impact both patient outcomes and quality of life (QoL). During this symposium, leading vasculitis experts considered the key challenges of managing patients with AAV in the real-world, focusing on the need to balance disease control against the known clinical risks associated with prolonged and high-dose GC exposure. A potential future role for complement-targeting agents within the AAV treatment paradigm was also discussed, based on new insights into complement-driven disease pathogenesis. These agents may help address an important unmet need which currently exists within AAV for effective therapies with an improved safety profile.

Ideal World Versus Real-World: Vasculitis Remission and Risk of Relapse in Europe

Neil Basu

Systemic vasculitis is the most heterogenous of all disorders, with the numerous different subtypes classified according to blood vessel size.[4] Granulomatosis with polyangiitis (GPA) is defined pathologically by necrotising granulomatous inflammation, and is associated with antibodies to proteinase 3, while its sister condition, microscopic polyangiitis (MPA), is associated with antibodies to myeloperoxidase.[4] Both diseases can affect any part of the body but have a predilection for the

ear, nose, and throat system, lungs, kidneys, skin, and joints.

Outcomes for patients with MPA and GPA have been transformed over recent decades, although premature mortality is still evident compared with the general population.[5,6] This transformation in vasculitis mortality can be largely attributed to cyclophosphamide, explained Basu: an important drug, but one that carries serious complications such as infections and cancers if used long term. Several multicentre randomised controlled trials have therefore evaluated ways of using cyclophosphamide more intelligently, including the pivotal CYCAZERAM study in which long-term cyclophosphamide therapy was replaced with azathioprine.[7] In this European trial, 155 patients with AAV who had reached remission with cyclophosphamide were randomised to either continue cyclophosphamide or switch to azathioprine.[7] After 18 months, no difference in relapse-free survival was seen between the two arms.[7] Other studies have explored strategies to further minimise cyclophosphamide dose, including the CYCLOPS trial that compared oral with intravenous cyclophosphamide and found both approaches to be similarly effective in controlling AAV.[8]

As well as azathioprine, there are other maintenance agents in the toolbox to help maintain remission, continued Basu. The French WEGENT trial demonstrated similar efficacy of methotrexate to azathioprine in maintaining relapse-free survival in AAV, while the EUVAS IMPROVE trial showed azathioprine was superior to mycophenolate in relapse prevention.[9,10] More recently, a number of trials have also confirmed a key role for rituximab as a maintenance agent. The MAINRITSAN study showed rituximab 500 mg 6 monthly was superior to daily azathioprine in maintaining remission, while the RITAZERAM trial, which focused on relapsing patients using 1 g rituximab every 4 months, confirmed this superiority.[11,12] It is important to note that, in both trials, relapse rates began to accrue again after rituximab therapy was completed.

Results from key randomised controlled trials have been synthesised into evidence-based AAV treatment guidelines; however, Basu stressed that problems still occur in this 'ideal world' guidelines-directed management of patients.[3] Relapse remains a common event, with combined follow-up from EUVAS trials showing a 50% relapse rate at 7 years.[13] Premature mortality also poses an ongoing issue, not because of the disease itself, but events such as serious infection in the first year, and cardiovascular disease and cancer thereafter.[6] In the 'ideal world' it is difficult enough trying to balance the fear of disease with the fear of drug toxicity, explained Basu, but in the 'real-world' clinicians face numerous additional challenges, including drug access, lack of multidisciplinary team care, diagnostic delays, and patient comorbidities.

To examine this real-world AAV treatment landscape, a retrospective, observational study was recently carried out across five European countries.[14] It involved 493 physicians from the European Union (EU) and 1,478 patients with AAV, followed from induction to 36 months maintenance, of whom 51% had MPA and 49% GPA. Mean patient age was 54.2 years, 56% were male and 44% exhibited severe progressive disease. The profile of drugs used for induction therapy was found to be similar across different countries, mostly cyclophosphamide and rituximab, although Basu described it as 'surprising' to see up 15% of patients receiving steroids alone for induction. At the start of maintenance, around 50% of patients were still not in full remission, in contrast to evidence from clinical trials which suggests that approximately 85% of patients achieve full remission by 3–6 months (Figure 1).[14] He suggested that this disconnect could be explained by different definitions of maintenance used by physicians and inter-country differences in practice, for example, 22% of patients were receiving cyclophosphamide in Germany at the start of maintenance compared with only 9% in the UK.[14] After 36 months of maintenance, this real-world study revealed that a significant number of patients had still not experienced full remission, and some remained on long-term cyclophosphamide (e.g., 12% in Germany). Use of high-dose oral steroids for prolonged time periods was also a common theme across the vasculitis disease course, with around 20–40% of European patients remaining on GC doses ≥7.5 mg for up to 36 months.[14]

In another insight into real-world AAV outcomes, Basu shared data from the Scottish AAV Linkage study in which 563 patients with classifiable AAV from different regions were identified and matched with general population controls.[15]

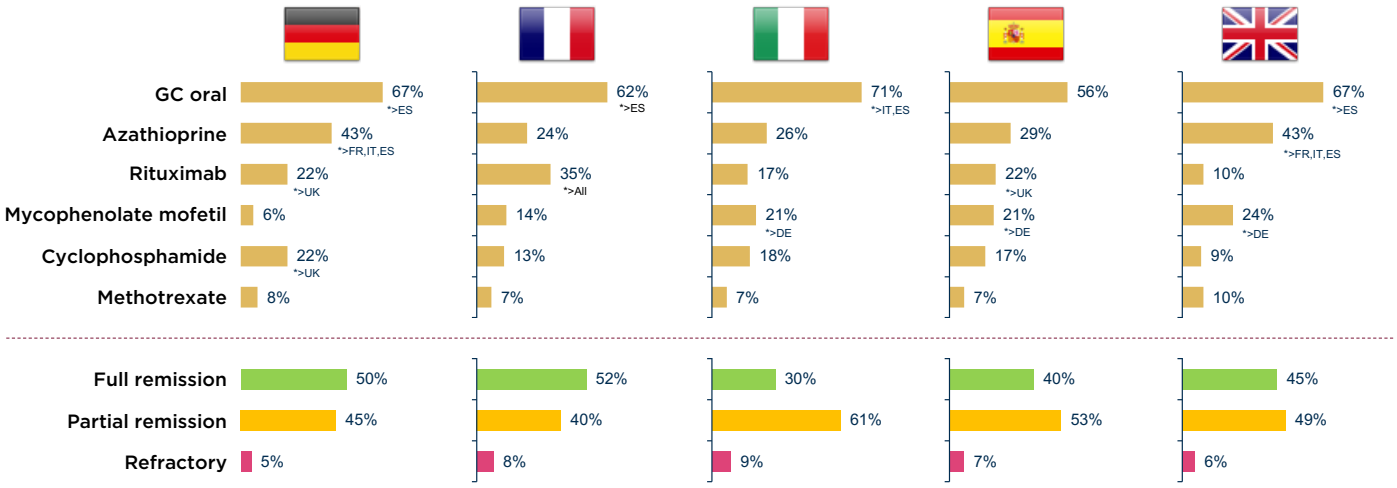

Figure 1: Real-world clinical practice study: treatment and outcomes at the start of maintenance in AAV.[14]

*Base: maintenance patients DE=300, FR=278, IT=300, ES=300, UK=300.

DE: Germany; ES: Spain; FR: France; GC: glucocorticoid; IT: Italy.

Compared with controls, patients with AAV exhibited an excess risk of numerous comorbidities including osteoporosis, cardiovascular disease, diabetes, and hypothyroidism. Infections rates were also higher in patients with AAV versus controls over an 8-year period, with the increased risk of infection most pronounced at diagnosis when patients were receiving induction treatment. The cumulative effect of comorbidities also proved greater than their sum, noted Basu, as evidenced by the degree of excess multimorbidity amongst patients with AAV in this study over time compared with the matched general population.[15]

Looking at the impact of vasculitis on real-world patient QoL, a recent UK-based study evaluated QoL, measured by the Short Form Health Survey with 36 items, in 470 patients with AAV versus 318 matched controls.[16] Across most domains, patients with AAV had significantly inferior QoL compared with the general population and were 2.5 times and over 11 times more likely to experience poor mental and physical QoL, respectively.[16] This impairment in QoL in patients with AAV appears comparable with that of other significant chronic diseases such as RA, lupus, and dialysis. Poor QoL in AAV can be driven by multiple, complex factors including clinical factors such as steroids and psychosocial factors like depression, anxiety, and fatigue.[16]

Heterogeneity of practice in the management of AAV also exists, as evidenced by a recent systematic review and meta-analysis of 10 studies that found significant variability in mortality data across different cohorts.[17] These disparities may stem from differences in levels of specialisation, the degree of multidisciplinary team involvement, and availability of fast-track access.

Overall, Basu concluded that a disconnect exists between current clinical practice and treatment guidelines in the management of AAV, which may relate to both heterogeneous disease and practice. Despite significant process, patients with AAV therefore continue to experience premature mortality, excess multimorbidity, and poor QoL.

Drivers of Disease in AAV: Pathophysiology, the Role of Complement, Treatment, and What Comes Next?

Peter Lamprecht

Peter Lamprecht explored disease drivers in AAV, focusing on the role of complement activation and inhibition. The complement cascade can be activated by three different pathways, classical, lectin, and alternative, leading to generation of

so-called anaphylatoxins, C3a and C5a, which have the ability to activate immune cells via interaction with key cell-surface receptors.[18] Lamprecht highlighted the activation of neutrophils via binding to the C5a receptor as particularly critical to the pathogenesis of AAV.

AAV itself is a small-vessel vasculitis in which neutrophils adhere to the endothelial cell layer and degranulate, inducing vessel-wall necrosis.[19] Looking more closely at the underlying pathogenesis, Lamprecht pinpointed neutrophil-expressed proteinase 3 (PR3) and myeloperoxidase (MPO) as the "prime autoantigens of disease."[20] Against a background of genetic predisposition and environmental factors, an immune response against these autoantigens is induced in patients with AAV.[20] Plasma cells then generate ANCA, which interact with MPO and PR3 on the cell surface of cytokine-primed neutrophils.[20] This induces neutrophil activation close to the endothelial cells, a highly pathologic event leading to endothelial cell damage and subsequent vasculitis.[20]

For a long time, the role of complement in the immune processes leading to AAV was unclear but experimental models have helped to shed light on its key pathogenic role. The first evidence for the role of complement in AAV was provided by a murine glomerulonephritis (GN) model in which MPO–ANCA generated in MPO knockouts was transferred to wild-type mice and was shown to induce crescentic GN.[21] Similar experiments demonstrated induction of crescentic GN using C4 knockout mice.[21] As C4 is part of both the classical and lectin complement pathways, these findings confirmed that neither pathway is needed for induction of GN with MPO–ANCA.[21] In contrast, there was no induction of GN by MPO–ANCA when the experiments were repeated in both factor B and C5 knockout mice, providing proof that the alternative pathway and complement C5 are essential.[21]

An extension of this model was used to confirm the key role of the C5a receptor (C5aR) in a generation of GN, with C5aR knockouts showing no GN as compared with wild-type animals.[22] Further experiments using mice carrying the human C5aR, treated with the inhibitory drug CCX168, showed induction of glomerular crescents by anti-MPO (39.3%), and anti-MPO and vehicle (30.5%), but very little crescentic GN with anti-MPO plus CCX168 (3.28); thus demonstrating that an oral inhibitor of the C5aR was able to ameliorate MPO–ANCA-induced GN.[22]

Other research has sought to decipher exactly how the alternative complement pathway is activated in AAV. In these experiments, normal TNF primed neutrophils were first incubated with IgG then the supernatant was reacted with normal serum. Activation of complement was measured by C3a generation, expressed as a percentage of the mean of the results for control IgG. Adding anti-MPO or anti-PR3 IgG elicited significantly higher C3a generation at 173% and 146% of control, respectively, whereas IgG from healthy controls had no impact.[21] These findings suggest that stimulation of neutrophils by ANCA causes release of factors that activate complement via the alternative pathway.

In actual patients with AAV, different complement profiles are evident. For example, increased levels of factor Bb are seen in patients with MPO AAV in remission but not PR3 AAV. In contrast, high C5a levels are found in both active PR3 and MPO AAV, and C3a is elevated in the plasma in MPO and PR3 AAV during active disease and remission. C4d, a fragment of the classical pathway, appears elevated in PR3 AAV.[23] Staining of human tissue for factor Bb, C3d, and C5b-9 has shown elevated levels in both the glomerula and small vessels as compared with non-AAV controls.[24]

Levels of factor H, a key inhibitor of alternative pathway activation, are decreased in active AAV compared with normal controls, but increase again when patients attain remission.[25] Interestingly, factor H is also correlated with renal prognosis in AAV, with low factor H levels in the plasma associated with reduced renal survival.[25] Research led by Lamprecht's own group has shown that anti-C5aR antibodies, which occur naturally in the circulation, are decreased in patients with AAV.[26] In a study of 110 patients with GPA and MPA, lower anti-C5aR levels were linked with higher disease activity, as denoted by the Birmingham Vasculitis Score (BVAS), and this correlated inversely with C5a levels in the plasma. Anti-C5aR antibody levels above and below the cut-off of 0.45 U/mL were also associated with major and minor relapses for both groups of patients with PR3–ANCA+ and MPO–ANCA+ AAV.[26]

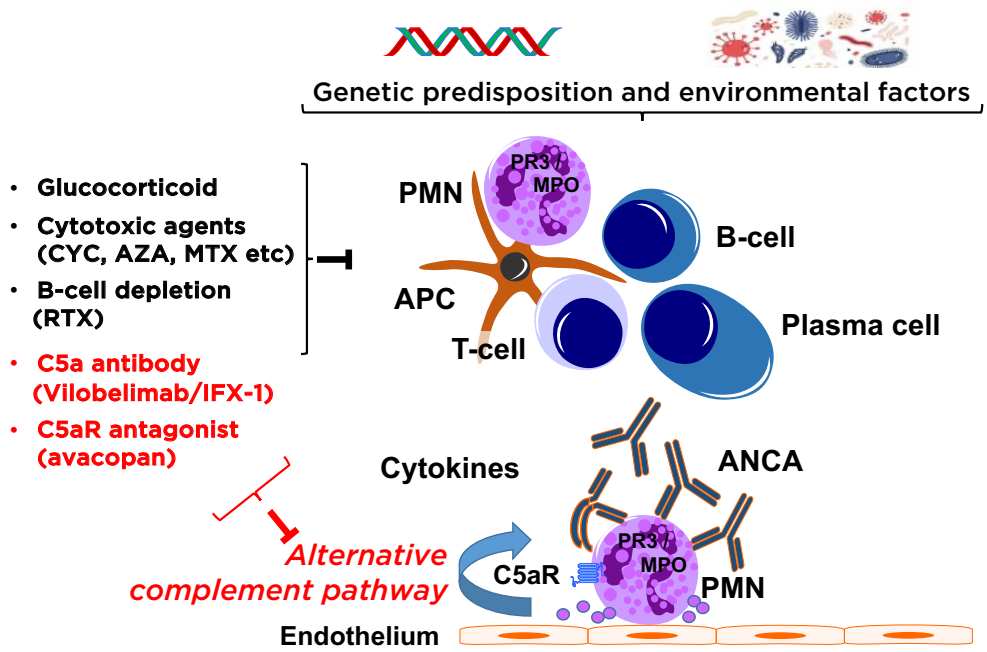

Figure 2: Pathogenesis and complement-targeting therapeutics in AAV.[22]

AAV: ANCA-associated vasculitis; ANCA: anti-neutrophil cytoplasmic antibody; APC: antigen-presenting cell; AZA: azathioprine; C5aR: C5a receptor; CYC: cyclophosphamide; MPO: myeloperoxidase; MTX: methotrexate; RTX: rituximab; PMN: polymononuclear neutrophil; PR3: proteinase 3.

Moving on to consider therapeutic targets in AAV, Lamprecht explained that classical treatment with GCs and cytotoxic agents inhibits lymphoproliferation and thereby modulates the adaptive immune response against ANCA targets, while rituximab offers more targeted B-cell depletion. New agents targeting the pathogenesis of AAV by specifically inhibiting the alternative complement pathway are also undergoing clinical development (Figure 2).

Phase II trials of the C5a antibody vilobelimab (IFX-1) are currently recruiting[27,28] and a published Phase III trial of the C5aR antagonist avacopan has shown it to be an effective GC-sparing agent in induction of remission in AAV.[29,30] A range of other candidates targeting different factors in the complement cascade are also undergoing evaluation in Phase I–III trials in AAV and other glomerular diseases.[29]

Summing up, Lamprecht explained that ANCA-induced neutrophil activation results in endothelial damage and activation of the alternative pathway of the complement system, especially in MPO AAV, but also in PR3 AAV, which differ with respect to their complement profiles. Regulators of the complement pathway such as factor H and anti-C5aR antibodies are decreased in AAV, indicating strong dysregulation of the complement system. Moving forward, inhibitors targeting the complement system at different levels and pathways could offer important new therapeutic options for patients with AAV.

The Real-World: A Case Study on the Risks of Glucocorticoids

Aladdin Mohammad

Updated global data on the epidemiology of AAV indicate that both incidence and prevalence are continuing to climb.[31] European prevalence currently ranks highest in Norway at 261 cases per 1 million population, followed by the USA at 218 and the rest of the world in the range 24–196.[31] Prevalence represents an important measure of the global burden of disease and denotes the number of patients who require clinical care and good treatment options, explained Mohammad. Recent studies from across Europe also suggest that the age-specific incidence of AAV is shifting higher, with peak age at diagnosis now standing at over 75 years.[31]

GCs occupy a central pillar in current European League Against Rheumatism (EULAR)/European Renal Association–European Dialysis and Treatment Association (ERA-EDTA) treatment guidelines for AAV but a number of important questions remain unanswered, such as: what constitutes the optimal dose at induction and what is the best tapering schedule? The EULAR recommends tapering of prednisolone or equivalent to 7.5–10.0 mg by Week 12.[3] However, in key clinical trials, the average dose of daily prednisolone was actually found to be 10 mg after 19 weeks and 7.5 mg after 21 weeks.[3] This is in a trial setting where adherence to the tapering protocol would be expected as very good, stressed Mohammad; in real-life practice we are dealing with patients with repeated relapses and longer time periods of observation. He showcased results from his own hospital, illustrating the potential benefits of a reduced-dose GC schedule such as PEXIVAS which led to lower cumulative doses of oral GCs, with an average saving of around 2 g in the first 52 weeks of treatment.[32]

Other important outstanding questions relate to the threshold in dose safety for patients on long-term GC treatment and the need for methylprednisolone (MP) pulse therapy. The viewpoint from the EULAR task force is that GC doses ≤5 mg/day pose an "acceptable low level of harm" but at >10 mg/day the risk of harm becomes elevated.[33] At intermediate doses, risk remains uncertain and patient-specific characteristics need careful consideration.[33] On the role of MP pulse therapy, findings from a retrospective USA/European study of 114 patients with newly diagnosed severe AAV found no difference in survival in patients who received MP pulse therapy, but a significantly higher incidence of infections, severe infections, and new-onset diabetes compared with those who did not.[34]

Mohammad went on to outline some of the key evidence, demonstrating the impact of long-term GC exposure on patients with AAV. Data from 296 patients involved in four EUVAS trials revealed that mean length of GC use was 40.4 months, in stark contrast to guideline recommendations to taper/stop steroid by Month 6.[35] A high level of organ damage was independently associated with increased cumulative GC use (p=0.016) and patients with longer duration of GC use were more likely to have a total Vasculitis Damage Index (VDI) score >5.[35] Severe treatment-related damage was linked to both frequency and duration of GC use.[35] Another important aspect to consider is the extent and pattern of organ damage in AAV. A population-based study of 86 patients followed for a median of 9 years showed that real-life treatment-related damage occurred frequently and was significantly more common in older patients (>65 years).[36] A further retrospective study from three European countries focusing specifically on elderly patients ≥75 years at diagnosis found that cumulative MP dose was associated with treatment-related damage (odds ratio: 1.25) and cumulative oral prednisolone dose was predictive of death due to infection.[37] Osteoporosis, cataracts, and diabetes all consistently ranked among the leading manifestations of treatment-related damage due to GCs across the various studies presented.[35,37]

Addressing the impact of GC exposure on the occurrence of comorbidities, Mohammad discussed data from two population-based, matched-control studies. Rate ratios of comorbidities were shown to be significantly higher for patients with AAV versus controls, most notably osteoporosis (rate ratio: 4.6–8.0), diabetes (rate ratio: 2.0–2.1), and hypertension (1.4–2.4), and occurred early during the disease course.[38,39] GC therapy was also found to be one of the key factors associated with severe outcomes (odds ratio: 3.7) in a multicentre UKIVAS cohort study involving 65 patients with systemic vasculitis diagnosed with COVID-19.[40]

In summary, Mohammad noted how the epidemiology landscape of AAV is shifting towards higher prevalence and more patients are living with these diseases; many of them elderly. GCs constitute one of the cornerstones of treatment, but a number of important clinical questions remain unanswered, most notably around the balance of dose and risk. What is certain is that prolonged use of GCs is associated with higher rates of severe organ damage and comorbidities, worse outcome from infections, and increased mortality. GCs undoubtedly have beneficial effects in AAV treatment regimens, Mohammad concluded, but an important unmet need persists for alternative therapies with improved efficacy and safety.

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Striking the Right Balance in Anti-neutrophil Cytoplasmic Antibody-Associated Vasculitis

This symposium took place on 4th June 2021, as part of the European Alliance of Associations for Rheumatology (EULAR) virtual congress

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Meeting Summary

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) causes irreversible short- and long-term damage to vital organs, particularly the kidneys and lungs. Current standard of care (SOC) for AAV, of which glucocorticoids (GC) are a lynchpin, has a number of important limitations: responses to therapy are variable, some patients fail to achieve and sustain remission, and treatment related adverse events (AE) are common. GCs in particular carry a heavy toxicity burden leading to increased organ damage and other serious AEs, as well as negatively impacting patients' quality of life. During this symposium, leading vasculitis experts considered how to strike the right balance in AAV and achieve the dual clinical priorities of sustained disease control and minimisation of treatment-related toxicity. The emerging evidence for alternative complement pathway activation in AAV disease pathogenesis and its investigation as a potential therapeutic target were also discussed, with promising results from the landmark Phase III ADVOCATE trial having recently demonstrated the non-inferiority of the novel C5a-inhibitor avacopan versus SOC at Week 26 and the superiority at Week 52.

The Pathogenesis of Vascular Lesions and the Alternative Complement Pathway

Benjamin Terrier

AAV are a type of small-vessel necrotising vasculitis that manifest as systemic diseases, with pulmonary; ear, nose, and throat; and renal involvement. The key pathological feature of AAV is the presence of ANCA, which can target two neutrophil antigens, myeloperoxidase (MPO) and proteinase 3 (PR3). Granulomatosis with polyangiitis is more commonly associated with PR3, while microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (previously known as Churg-Strauss) are typically associated with the MPO serotype.

Terrier discussed how the pathogenic role of MPO-ANCA was first demonstrated two decades ago. Treatment of mice with MPO-ANCA purified from MPO-deficient mice or via transfer of splenocytes into immunodeficient mice was shown to induce a glomerular nephritic disease after 6 days. The glomeruli of these mice exhibited a fibrinoid necrosis with crescents with very few IgG deposits, indicating a pauci-immune glomerular nephritis as seen in the human disease.[1]

Further work then set out to explore the role of neutrophils in disease pathology. An important genome-wide association study demonstrated that there is a distinct genetic background according to ANCA specificity, with PR3 ANCA patients, but not MPO-ANCA patients, showing polymorphisms of key genes encoding α-1 antitrypsin and PR3.[2] Neutrophils have also been established as a key effector of endothelial damage in AAV. Analysis of the characteristics of neutrophils in patients with AAV revealed specific gene expression profiles, specifically disturbed epigenetic control of PR3/MPO expression.[3-5] *In vitro* data demonstrated that MPO and PR3 are able to induce a proinflammatory environment in endothelial cells, including the production of proinflammatory cytokines, while *in vivo* experiments have shown that ANCA is able to stabilise the endothelial adhesion of neutrophils and increase their transmigration, thereby driving inflammation.[6-10]

The neutrophil antigen PR3 has also been proven to play a key role in the inflammatory process that underpins AAV. Patients with AAV show constitutive expression of membrane PR3 (mPR3), which acts as a danger signal for macrophages and disrupts immune signalling. Apoptotic neutrophils expressing mPR3 induce a proinflammatory response by macrophages, which then induces maturation and activation of dendritic cells, creating a favourable microenvironment for the persistence of inflammation.[11-13]

The complement pathway has emerged as another potential culprit with a role in AAV pathophysiology. In a murine model of MPO-ANCA vasculitis induced by intravenous injection of MPO-ANCA, mice pre-treated with cobra venom factor (a toxin that depletes complement) did not develop renal disease.[14] This clearly illustrates the critical importance of the complement pathway in disease initiation, noted Terrier. Further work in mice with a different genetic background showed that those missing genes from the alternative complement pathway, particularly C5 or factor B, were protected from developing vasculitis in the kidney, suggesting that ANCA-stimulated neutrophils release factors, which activate complement via the alternative pathway.[14] Mice with deleted C5a pathway genes, particularly those coding for the C5a receptor, were similarly protected from MPO-ANCA glomerular nephritis and animals treated with CCX168, a molecule that specifically inhibits the C5a receptor, developed less severe forms of the disease as evidenced by decreased haematuria, proteinuria, and leukocyturia.[15]

Research into AAV also has probed the interaction between activated neutrophils and factor H. TNF-primed neutrophils exhibit a strong inflammatory reaction when bound to endothelial cells, including respiratory burst and degranulation. Binding factor H to these neutrophils acts to inhibit ANCA-induced neutrophil activation. However, in patients with AAV, factor H displays a deficient ability to bind to neutrophils and inhibit their ANCA-induced activation.[16]

Integrating all of these different mechanistic aspects gives a clear insight into the interconnected role of ANCA, neutrophils, and

complement in AAV.[17] Activation of neutrophils by cytokines or C5a induces membrane expression of MPO/PR3 antigens. These primed neutrophils then undergo activation by ANCA, inducing an oxidative burst and endothelial damage. Activated neutrophils in turn release factors that activate the alternative complement pathway, leading to production of C5a and further amplification of the inflammatory response. The result is a positive inflammatory feedback loop.[17] Terrier noted that, from a therapeutic perspective, targeting activation of the alternative complement pathway, in particular the key C5a/C5a receptor interaction, could be clinically beneficial and is one of the primary approaches currently under evaluation.

Overall, Terrier concluded that emerging evidence from murine models, human correlation studies, and data from randomised controlled trials support a key role for the alternative complement pathway in AAV. There are also strong interactions between neutrophil activation and their ability to activate the complement pathway, creating the possibility of combination therapies that target both. Potential therapeutic targets within the complement pathway include blockade of complement activation by C5a/C5aR inhibitors, which is emerging as a very promising strategy, noted Terrier. Other future complement-targeting approaches may include restoration of the regulator function of factor H.

Glucocorticoids in ANCA-Associated Vasculitis: Clinical Efficacy and Short-Term Risks. Where Do We Stand?

Joanna Robson

GCs are recommended at every stage of the European Alliance of Associations for Rheumatology (EULAR) management pathway for AAV as induction therapy, treatment for organ or life-threatening disease, as maintenance agents, and to manage relapse.[18] GCs therefore represent a constant in patients' lives, explained Robson, and exert a direct impact in terms of outcomes, AEs, and quality of life.

From a historical perspective, mortality remained high when GCs were the only available treatments for AAV.[19] Today, the increased risk of infection associated with high-dose GCs remains a key concern for clinicians and is underscored by data from observational studies. A Japanese study showed that patients on high-dose GCs had a 50% cumulative incidence of severe infections over the course of 1 year.[20] In another retrospective, multicentre study (n=114) from Europe and the USA, intravenous methylprednisolone significantly increased the risk of infection during the first 3 months (hazard ratio: 2.7; 95% confidence interval: 1.4–5.3), even after adjustment for confounding factors.[21] Evidence from this same study also showed no benefit of methylprednisolone pulses versus standard-dose GC therapy in terms of survival, renal recovery, or relapses.[21]

Robson showcased data from a recent systematic literature review of 91 studies (published between 2000 and 2020), which included 18 randomised controlled trials and encompassed over 10,000 patients with AAV, highlighting the severe AEs associated with GC use. Infections were found to be the overwhelming risk, noted Robson, but other severe AEs were also of concern such as gastrointestinal haemorrhage or ulcers and musculoskeletal disorders.

In long-term follow-up of six randomised European Vasculitis Society (EUVAS) trials (n=302), almost one-half (48%) of patients were still receiving GCs after 7.3 years from diagnosis, which reflects the reliance on these drugs in clinical practice.[22] Damage related to active vasculitis and its treatment were also shown to increase over time, with several of the most frequent Vasculitis Damage Index (VDI) items attributable specifically to steroids.[22]

Turning to patients' perspective of steroids, Robson explained her involvement in a multinational project to develop a robust and well-validated patient-reported outcome (PRO) measure for AAV.[23] The resulting AAV-PRO contains six different domains: organ-specific symptoms, systemic symptoms, treatment side effects, social and emotional impact, concerns about the future, and physical function; all of which individually fit the Rasch model and show good internal consistency.[23] Specifically,

Rasch analysis revealed treatment-related side effects as being of great importance to patients (p=0.065), with the underlying constructs (e.g., concern about appearance, weight gain, sleep problems, gastrointestinal complaints, and skin issues) all related directly to steroids.[23] A secondary analysis of the quantitative data from this study specifically explored patient perceptions of GC therapy in AAV.[25] Results showed a complex pattern across the patient journey.[24] As Robson explained, at diagnosis patients often feel relief or gratitude when starting on GCs, which exert a swift effect on their symptoms. However, short-term AEs are common experiences that quickly lead to patients developing fears about the potential long-term impact of GCs. This can be fuelled by the negative connotations around steroid use from family, friends, and wider society. As AAV enters the chronic stage, the 'weighing up' process of GC benefits versus risks becomes even more pronounced and can impose a substantial cognitive burden on patients. Patients come to depend on steroids for their health, explained Robson, so must balance fears around ongoing and future GC AEs against the fear of a potential disease flare-up if steroid doses are reduced.

An earlier study into the burden of disease in AAV also identified treatment-related aspects as of key importance to patients.[25] Frequent burdens identified in this study, such as fatigue or energy loss, weight gain, financial or work issues, and anxiety, could be linked directly to steroid use.[25] Looking at health-related quality of life (HrQoL) in AAV, symptoms of depression and anxiety have been found to be highly prevalent, affecting 25.5% and 42.3% of patients, respectively.[26] In qualitative surveys, patients described high-dose GCs as a direct contributor to this adverse HrQoL, with positive improvements seen as doses were reduced. The association of specific factors with work disability among working-age patients with AAV has also been explored in a cross-sectional study (n=208). Independent predictors were fatigue (odds ratio [OR]: 7.1), which can be linked to poor sleep caused by GCs, being overweight (OR: 3.4), and depression (OR: 4.4).[27]

The OMERACT Glucocorticoid Working Group is an international consensus body that is developing a core outcome set for future clinical trials involving GCs. Domains include hard clinical end-points that can be well-measured using the GC toxicity index (e.g., hypertension and diabetes) plus more patient-focused outcomes such as appearance, sleep disturbance, and mood disturbance.[28] Robson explained that the Working Group have identified a critical gap in this area as currently there is no instrument available to accurately categorise these PROs and measure them effectively in a clinical trial setting. To plug this gap, work is underway to develop a steroid PRO capable of capturing patient perspectives on GCs for rheumatic diseases. This project will consist of initial qualitative interviews with over 50 patients from the UK, USA, and Australia, followed by a larger-scale survey to determine final scale structure and measurement properties/validation.

In summary, although GCs constitute effective treatments for AAV, they are associated with a range of short- and long-term AEs. Consequently, there is an impact on HrQoL, not only from AAV disease itself but also from treatment. It is important to consider and measure this impact of GCs from both physician and patient perspectives, Robson concluded.

Getting the Balance Right: Emerging Therapies in ANCA-Associated Vasculitis

Bernhard Hellmich

AAV is a rare disease, but recent data indicate that both prevalence and incidence are increasing. Based on retrospective, longitudinal analysis of health insurance data from >3 million Germans, the prevalence of granulomatosis with polyangiitis and microscopic polyangiitis currently stands at 256 per 1 million, with an annual incidence of 46 per 1 million.[29]

Hellmich outlined evidence for the outcomes obtained with current induction therapies recommended in EULAR AAV management guidelines.[18] Long-term survival data from four randomised EUVAS trials showed that mortality in patients treated with standard therapy was high (OR: 2.6), with the main causes of death in the first year being uncontrolled vasculitis

(19%) and infections (48%).[30,31] The question of whether outcomes could be improved by plasma exchange or GC sparing were addressed in the PEXIVAS trial, the largest study ever conducted in AAV, which enrolled 704 patients with severe disease followed for up to 7 years.[32] Plasma exchange had no significant impact on the primary composite end-point of death and end-stage renal disease at any timepoint in the study. However, reduced-dose GC proved non-inferior to standard-dose/taper over the whole study period and was associated with a significantly lower risk of serious infections in the first year (27% versus 33%).[32]

"If lower-dose GCs work, then can patients potentially be managed with no steroids at all?" asked Hellmich. This challenging hypothesis was recently addressed in two studies investigating the C5a receptor antagonist avacopan. The CLEAR, Phase II, proof-of-concept study enrolled 67 patients with active AAV and renal involvement who were assigned to one of three arms: standard therapy with high-dose GC, low-dose GC (20 mg starting dose) and avacopan, or avacopan and no GC.[33] The primary end-point of ≥50-point reduction in Birmingham Vasculitis Activity Score (BVAS) at Week 12 and no worsening in any body system was achieved in a similar proportion of patients in all three arms: 70.0%, 86.4%, and 81.0%, respectively. Disease activity, as measured by percent change in BVAS, decreased rapidly, with a faster decline seen in the avacopan groups as compared to the steroid-only arm.[33]

Promising results from this proof-of-concept study led to the design and conduct of the larger Phase III ADVOCATE trial of avacopan, the results of which were recently published in the New England Journal of Medicine.[34,35] ADVOCATE enrolled 300 patients with active AAV (either new disease or relapsing), who received standard induction therapy and were randomised 1:1 to avacopan 30 mg twice daily for 1 year plus placebo matching prednisone, or placebo plus prednisone starting at 60 mg/day and tapered to zero for 20 weeks. Patients were stratified according to baseline therapy (oral/intravenous cyclophosphamide or rituximab), ANCA type (anti-MPO or anti-PR3), and new or relapsing disease.[35] Overall, patients were well-balanced across study arms: mean BVAS score was approximately 16, indicating severe disease, and most patients had impaired renal function (mean estimated glomerular filtration rate [eGFR] of approximately 50 mL/min/1.73m^2).[35]

The dual primary end-points of ADVOCATE were remission at Week 26 and Week 52. In the avacopan group, 72.3% of patients achieved remission at Week 26 compared with 70.1% in the control SOC arm, confirming the non-inferiority ($p<0.0001$) of the avacopan-based regimen to GCs. At Week 52, the avacopan-based regimen proved superior to GCs, with 65.7% of avacopan-treated patients remaining in remission versus 54.9% on SOC; this difference was statistically significant ($p=0.0066$) (Figure 1).[35]

As would be expected with more patients sustaining remission, the relapse rate was also significantly lower in the avacopan arm versus SOC. Relapse rate was 10.1% with the avacopan-based regimen compared with 21.0% with SOC ($p=0.0091$), equivalent to a 54.0% reduction in relative relapse risk.[35] Significant improvements in renal function were also seen with the avacopan-based regimen. In approximately 80% of patients with renal disease at baseline, avacopan produced a better recovery of renal function compared to SOC, with the benefit particularly marked in those patients at the lowest tertile of the eGFR.[35] Deterioration in renal function is an indicator of worse prognosis in AAV, noted Hellmich.

In the ADVOCATE study, the mean total prednisone-equivalent dose of GCs was higher in the SOC group (3,655 mg) compared to the avacopan-based regimen (1,349 mg). However, the avacopan group was not GC-free, Hellmich pointed out, with additional sources including pre-randomisation GCs, which were then tapered, co-medication with rituximab, and off-protocol doses.[35] At both Weeks 13 and 26, avacopan-treated patients had a significantly lower cumulative burden of GC toxicity, as measured by the glucocorticoid toxicity index, versus SOC. A significant difference in toxicity between avacopan and SOC was also evident in aggregate improvement scores on the glucocorticoid toxicity index at Weeks 13 and 26 (Figure 2).[35]

Treatment	n (%)	Estimate of common difference in percentages	Two-sided 95% CI	Non-inferiority p value*	Superiority p value† (one-sided)
SOC (N=164)	90 (54.9)				
Avacopan-based regimen (N=166)	109 (65.7)	12.5	(2.6, 22.3)	<0.0001	0.0066

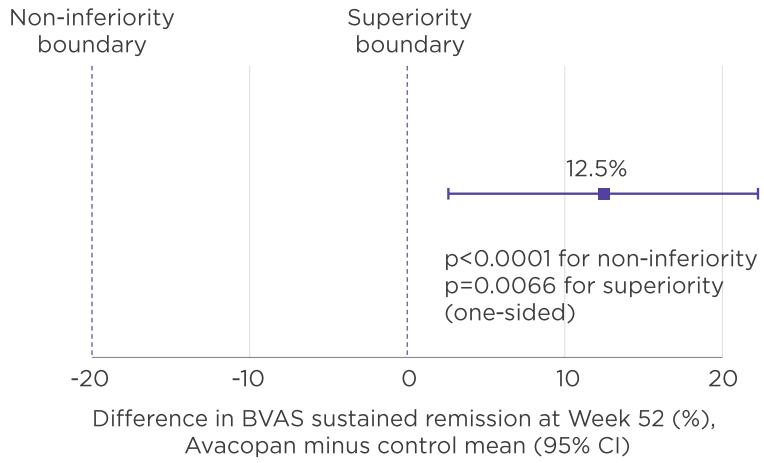

Figure 1: Avacopan was superior to glucocorticoids in sustaining remission at Week 52 (ADVOCATE primary end-point 2).[36]

*Boundary for non-inferiority <20%.

†Boundary for superiority <0%.

BVAS: Birmingham Vasculitis Activity Score (BVAS); CI: confidence interval; SOC: standard of care.

Overall, the improved GC-related toxicity profile with avacopan translated into a numerically lower rate of AEs compared to the SOC group; however, severe AEs occurred at a similar rate in both arms (23.5% versus 25.0%, respectively). Severe infections were also numerically lower in the avacopan group, but this did not significantly impact the number of deaths. Total GC-associated AEs occurred more frequently in the SOC group (80.5%) as compared to avacopan (66.3%).[35]

Hellmich then turned to the evidence supporting drugs for maintenance of remission in AAV. In the MAINRITSAN trial, rituximab (500 mg every 6 months) proved superior to azathioprine (tapered after 12 months), and was associated with a lower rate of relapse at Month 28.[36] More recent data from the RITAZAREM trial, which employed a higher dose of rituximab (1,000 mg every 4 months) versus azathioprine for 2 years, confirmed this significantly lower relapse risk with rituximab versus azathioprine.[37] Only 13% of rituximab patients experienced relapse by Month 24, compared with 38% on azathioprine. Rituximab was superior in preventing both minor and major relapses, and relapse risk was not influenced by ANCA type, relapse severity, or GC induction. No new safety signals emerged in the RITAZAREM trial.

"If rituximab is such an effective drug, should it really be stopped after 2 years as per EULAR recommendations?" questioned Hellmich. The placebo-controlled, extension study MAINRITSAN-3 set out to answer this question by randomising 97 patients to either stop rituximab after 18 months or continue treatment for an additional 18 months.[38] Patients on long-term rituximab showed a significantly lower relapse risk versus the control, with relapse-free survival rates at Month 54 (the primary end-point) of 96.0% versus 74.3%, respectively. After 36 months, rituximab therapy also proved 100.0% effective in preventing severe relapse to Month 54.

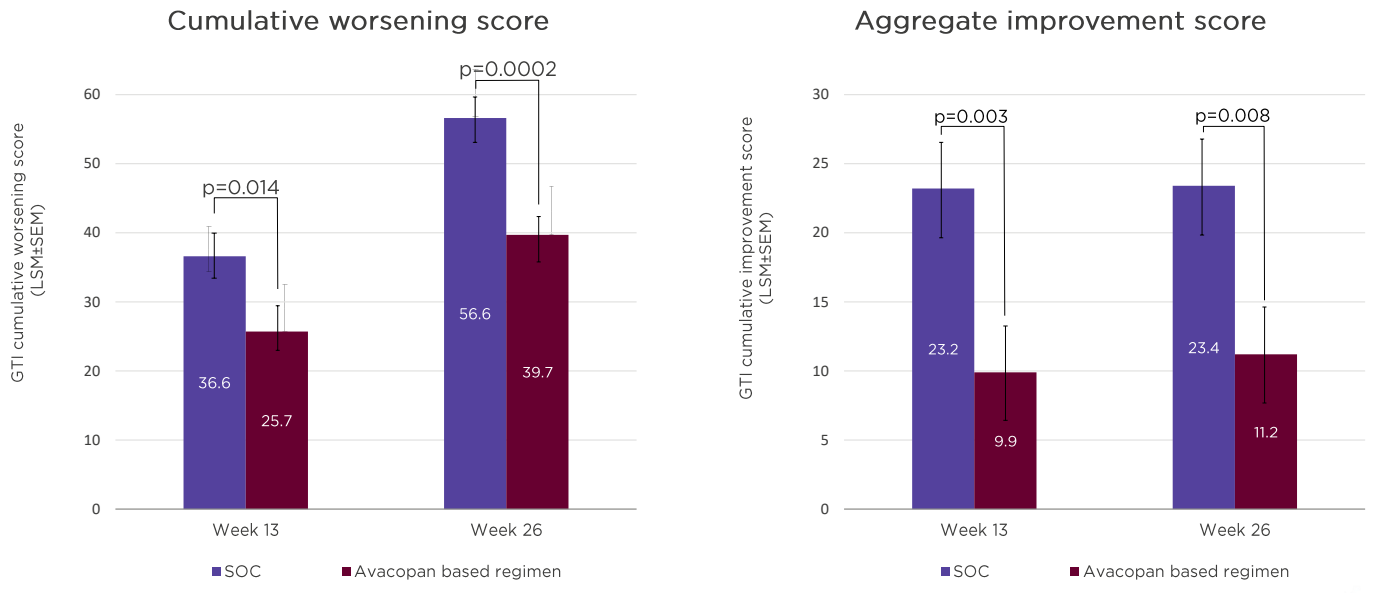

Figure 2: Glucocorticoid toxicity index scores in the ADVOCATE trial.[36]

GC: glucocorticoid; GTI: glucocorticoid toxicity index; LSM: least squares mean; SEM: standard error of the mean; SOC: standard of care.

No new safety signs occurred with long-term use of rituximab, and severe AEs (including infections) were similar across both arms.[38]

In summary, Hellmich reiterated that the key goals of therapy in AAV are to control disease activity and prevent permanent organ damage and treatment-related AEs. For the induction of remission, a reduced steroid protocol (in combination with standard rituximab or cyclophosphamide) is equally effective but benefits from fewer infections. We now also have the opportunity to use targeted therapy with avacopan, said Hellmich, which shows similar efficacy for induction of remission compared to GCs, with the added advantages of reduced relapse risk and a lower rate of GC-related AEs. For maintenance of remission, rituximab is superior to azathioprine, with treatment beyond 18 months affording further reductions in relapse risk.

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Abstract Reviews

Read on for summaries of abstracts presented at the EULAR 2021 virtual congress atherosclerosis burden and environmental air pollution in rheumatoid arthritis.

Differences in Low-Density Lipoprotein Particle Composition and Oxidation May Underlie the Paradoxical Association of Low Levels with Higher Coronary Atherosclerosis Burden in Rheumatoid Arthritis

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Keywords: Coronary atherosclerosis, CT angiography, low-density lipoprotein (LDL) oxidation, low-density lipoprotein (LDL) particle composition.

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BACKGROUND AND AIMS

The association between cholesterol and cardiovascular disease (CVD) risk is attenuated in patients with rheumatoid arthritis (RA).[1] In fact, patients with RA in the lowest low-density lipoprotein (LDL) group (<70 mg/dL) may experience an unexpectedly high CVD risk.[2] The authors explored whether patients with LDL <70 mg/dL (Group 1) had higher coronary atherosclerosis burden compared to other LDL groups (Group 2: 70≤LDL≤130 mg/dL; Group 3: LDL>130 mg/dL), as a reason for this risk. The authors further evaluated whether low LDL in Group 1 associated with differences in inflammation, LDL particle composition, or oxidation.

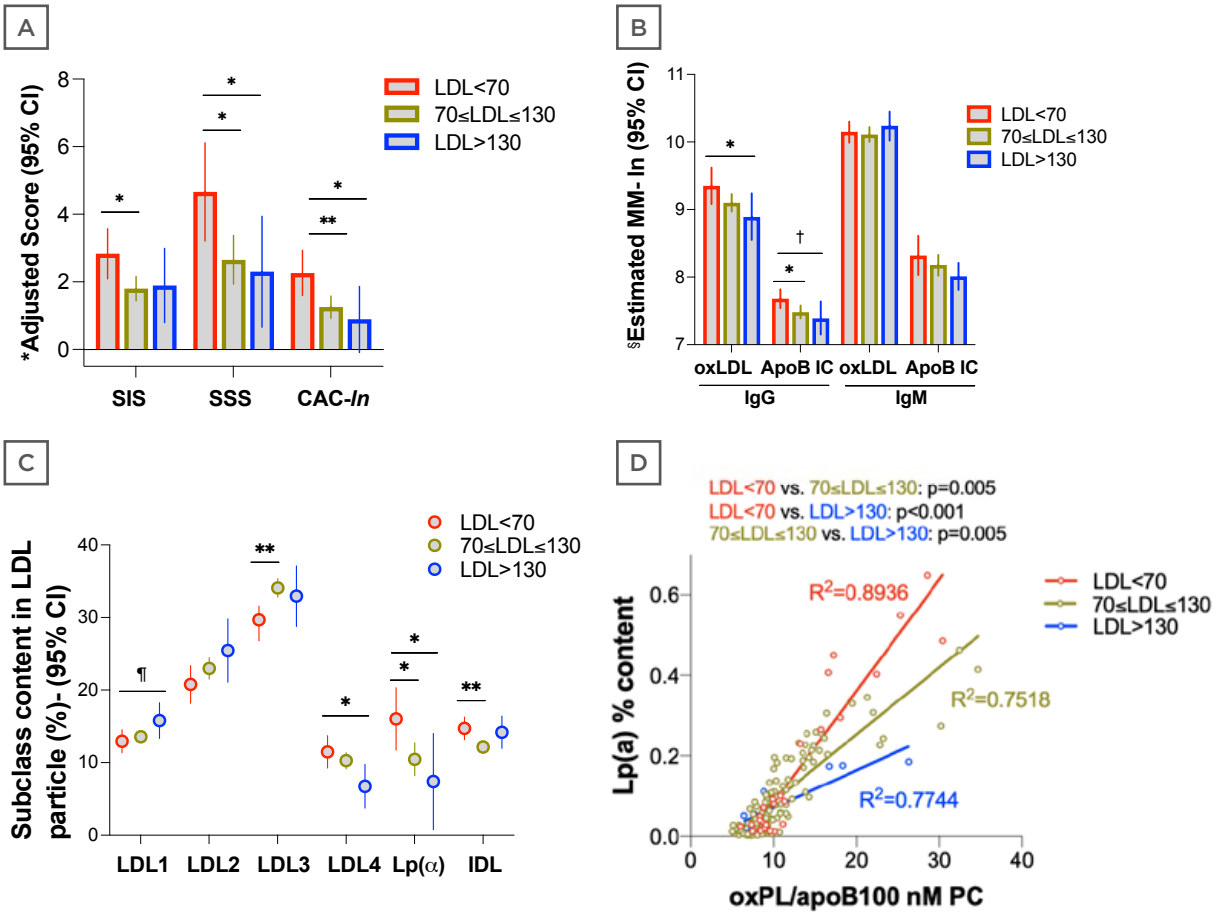

Figure 1: Coronary plaque burden, lipoprotein particle structure and oxidation differences across LDL strata in RA. **A)** Patients with LDL <70 mg/dL had higher coronary plaque burden compared to higher LDL groups. Model adjusted for Framingham D'Agostino risk score, obesity, DAS28-CRP, bDMARD use, and statin use. **B)** Patients with the lowest LDL exhibited greater serum levels of IgG anti-oxLDL and apoB100 IC than higher LDL groups. This was not the case for IgM anti-oxLDL and apoB100 IC. Model adjusted for Framingham D'Agostino risk score and statin use. **C)** LDL particle composition differs across various LDL groups. Model adjusted for Framingham D'Agostino risk score, statin use, and total HDL. **D)** The association between Lp(a) content and LDL oxidation appears stronger in patients with LDL <70 mg/dL compared to higher LDL groups. Models adjusted for Framingham D'Agostino risk score and statin use.

ApoB100 IC: apolipoprotein B100 immune comeplexes; bDMARD; biologic disease-modifying anti-rheumatic drugs; CAC-*ln*: log-transformed coronary artery calcium score; CI: confidence interval; DAS28-CRP: disease activity score-28 for rheumatoid arthritis with C-reactive protein; EMM: estimated marginal means; HDL: high-density lipoprotein; LDL: low-density lipoprotein; Lp(a): lipoprotein (a); nMPC: nonlinear model predictive control; oxLDL: oxidised LDL; oxPL: oxidised phospholipids; RA: rheumatoid arthritis; SIS: segment involvement score; SSS: segment stenosis score, p=0.056, † p=0.051, *p<0.05, **p<0.01

MATERIALS AND METHODS

One hundred and fifty patients with no history of CVD, from the previously described PROTECT-RA cohort,[3] underwent coronary atherosclerosis evaluation with CT angiography. Coronary artery calcium, number of segments with plaque (segment involvement score), stenotic severity (segment stenosis score), and extensive (>4 segments with plaque) or obstructive disease (>50% stenosis) were assessed. Lipoprotein classes and subclasses were directly measured using single vertical spin density gradient ultracentrifugation. Oxidised LDL (oxLDL) was measured with monoclonal antibody E06. Chemiluminescence ELISA quantified IgG and IgM antibodies to oxLDL (anti-oxLDL) and apolipoprotein (apo)B100 immune complexes (IC). Pro-inflammatory cytokines were measured

with Erenna® Immunoassay (Singulex, Alameda, California, USA). Robust linear and logistic regression models evaluated associations between LDL groups and plaque outcomes; both models were adjusted for Framingham modified cardiovascular risk score, obesity, disease activity, biological disease-modifying anti-rheumatic drugs, and statin treatment. Similar models evaluated adjusted differences in LDL subclasses, oxLDL, anti-oxLDL, anti-apoB100 IC, and cytokines across LDL groups.

RESULTS

Patients were predominantly female with seropositive, erosive, and well-controlled disease. Group 1 patients had higher coronary plaque burden (Figure 1A) and 2.8-times greater risk of extensive or obstructive disease (adjusted odds ratio: 2.82; 95% confidence interval [CI]: 1.12–7.17; p=0.031) compared to LDL >70 groups. No differences in RA-related inflammation were observed across LDL groups that could explain disparity in LDL levels. However, statin-naïve patients with LDL <70 mg/dL exhibited greater oxLDL (log-transformed estimated marginal means [EMM]: 2.55, 95% CI: 2.34–2.77; versus 2.27, 95% CI: 2.19–2.36, p=0.018 for LDL >70). Moreover, Group 1 patients exhibited greater serum levels of IgG anti-oxLDL and apoB100 IC than higher-LDL groups (Figure 1B). This was not the case for their IgM counterparts. LDL subclass-relative content in the LDL particles differed across groups (Figure 1C). Lipoprotein (a) (Lp[a]) was higher in LDL particles in Group 1 (EMM: 16.04%, 95% CI: 11.75–20.33; versus 10.48%, 95% CI: 8.20–12.75, p=0.026 in Group 2; and 7.41%, 95% CI: 0.77–14.04, p=0.033 in Group 3). Notably, Lp(a) content strongly associated with oxLDL overall (r=0.83; p<0.0001); this association was stronger for Group 1 compared to others (p<0.005; Figure 1D). Immune recognition of oxLDL, specifically IgG anti-oxLDL and anti-apoB100 IC, associated with higher TNFα and IL-6 elaboration. IL-6 was higher in Group 1 (log-transformed EMM: 1.98, 95% CI: 1.64–2.32; versus 1.57, 95% CI: 1.45–1.70, p=0.028 in Group 2; and 1.32, 95% CI: 0.84–1.80, p=0.031 in Group 3). IL-6 associated with both IgG anti-oxLDL (p=0.015) and anti-apoB100 IC (p=0.016). IL-6 further associated with higher coronary artery calcium (adjusted B [association between IL-6 and coronary artery calcium]: 0.41; 95% CI: 0.01–0.81; p=0.049).

CONCLUSION

Patients with RA with LDL <70 mg/dL had higher coronary atherosclerosis burden. Low circulating LDL in that group may reflect higher oxidation; this was mostly linked to the larger Lp(a)-relative content of LDL and the significantly higher oxidation potential in that group. Greater LDL oxidation and immune recognition of oxLDL further associated with higher IL-6 elaboration, which may in turn augment atherosclerosis burden in the low-LDL group. ■

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Association Between Environmental Air Pollution and Rheumatoid Arthritis Flares

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Keywords: Air pollution, flares, rheumatoid arthritis (RA).

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BACKGROUND AND AIMS

Environmental air pollution has been linked to the pathogenesis of rheumatoid arthritis (RA).[1] Nevertheless, there is no evidence linking higher concentrations of air pollutants with the risk of RA reactivations. The primary objective of this study was to determine the association between concentration of air pollutants and RA disease relapses. Revealing the possible connections between air pollutants and inflammatory arthritis severity and their chances to progress or relapse might help predict treatment response and healthcare utilisation of such patients.

MATERIALS AND METHODS

The study data on patients with RA was extracted from the registry of biological therapies at the University of Verona, Italy. The authors retrospectively collected longitudinal data of patients affected by RA starting from September 2013 to September 2018. They also collected data on the daily concentration of air pollutants in the Verona area from this time frame. The following air pollutant concentrations (μg/m^3) were available: carbon monoxide (CO), nitrogen oxide (NO), nitrogen dioxide (NO_2), nitrogen oxides (NO_x), particulate matter <10 μm (PM10), ozone (O_3), and particulate matter <2.5 μm (PM2.5).

The authors analysed the concentration of exposure to pollutants as area under the curve and mean concentration during the 30-day and 60-day periods before the appointment with the rheumatologist. The authors conducted a cohort cross-sectional analysis to determine the association between C-reactive protein (CRP) serum levels and the concentration of air pollutants. A case-crossover study can be used when brief exposures cause a transient change in risk of an acute-onset disease or reactivation of such diseases.[2] In case-crossover studies, instead of obtaining information from two groups (cases and controls), the exposure information is obtained by comparing two different periods of time in the same group of patients followed longitudinally.

RESULTS

The authors collected data from 888 patients with RA who had 3,396 follow-up visits and 13,636 daily air pollution records from June 2013 to September 2018. From the general cross-sectional analysis of the overall cohort, the authors found that patients in non-remission (≥2.6 and >3.2 disease activity score 28 [DAS28]-CRP) and high CRP (≥5 mg/L) were frequently exposed to greater concentration of air pollutants when compared to patients in remission or low disease activity (<2.6 or ≤3.2 DAS28-CRP) and patients with low CRP levels. Patients exposed to PM10 concentrations ≥50 μg/m^3 had a 70% higher risk of having CRP levels ≥5 mg/L (odds ratio: 1.696; 95% confidence interval: 1.245–2.311). Among patients with RA, 440 patients (49.5%) had at least two follow-up visits with a difference in DAS28-CRP of more than 1.2 points (with current DAS28-CRP ≥3.2) serving as the sample for the case-crossover study. All air pollutants concentrations were significantly higher in the hazard period when compared to control period (Table 1).

Table 1: Case-crossover study.

Pollutant (µg/m³)		Control period (low disease activity, n=440)	Hazard period (flare, n=440)	p value
CO	Mean	0.38	0.42	0.001
	AUC	22.00	24.53	0.001
NO	Mean	19.23	24.11	0.002
	AUC	1,120.53	1,403.88	0.002
NO_2	Mean	30.91	32.44	0.042
	AUC	1,800.96	1,892.05	0.040
NO_x	Mean	60.34	69.35	0.004
	AUC	3,515.77	4,041.06	0.004
PM10	Mean	31.21	33.65	0.011
	AUC	1,789.22	1,942.52	0.005
O_3	Mean	31.08	33.79	0.002
	AUC	1,776.37	1,934.35	0.001
PM2.5	Mean	23.08	24.74	0.018
	AUC	1,272.61	1,403.60	<0.001

Mean of concentrations (mean and the AUC) of air pollutants in the 60 days before low-disease activity and flare visit (DAS28-CRP difference >1.2).

AUC: area under the curve; CO: carbon monoxide; CRP: C-reactive protein; DAS28: disease activity score; NO: nitrogen oxide; NO_2: nitrogen dioxide; NO_x: nitrogen oxides; O_3: ozone; PM2.5: particulate matter <2.5 µm; PM10: particulate matter <10 µm.

CONCLUSION

The authors studied the association between air pollution and RA disease severity and reactivation in a cohort of patients followed longitudinally for more than 5 years. In patients with RA, the exposure to high levels of air pollutants (i.e., CO, NO, NO_2, NO_x, PM10, O_3 and PM2.5) was associated with increased CRP levels and higher risk of experiencing a flare of arthritis. ■

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Efficacy and Safety of TNF-α Antagonists and Tocilizumab in Takayasu Arteritis: Multi-centre, Retrospective Study of 209 Patients

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Keywords: Takayasu arteritis (TA), TNF-α antagonists, tocilizumab

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BACKGROUND AND AIMS

Takayasu arteritis (TA) is a chronic inflammatory large-vessel vasculitis, predominantly affecting the aorta and its main branches.[1] Vessel inflammation leads to wall thickening, fibrosis, stenosis, and thrombus formation. TA mostly affects females and many ethnic and racial groups worldwide. The treatment strategies are not well recognised and the place of glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs), and, more recently, of biological targeted therapies is still not determined.

MATERIALS AND METHODS

The authors conducted a retrospective multi-centre study in referral centres from France, Italy, Spain, Israel, Japan, Tunisia, and Russia about biological-targeted therapies in TA during the period from January 2017 to September 2019 for the data collection. All physicians were asked to fulfil standardised anonymised excel form. All patients met TA criteria for the American College of Rheumatology (ACR) and/or Ishikawa, modified by Sharma.[2] The patients' age, sex, associated diseases, TA duration and vascular extension (Numano scale), clinical, laboratory and imaging data, and treatments were analysed at baseline, at the initiation of each new treatment regimen, at 6 months and at the last available visit. Glucocorticoid dosages were analysed at the initiation of each new treatment regimen and during the follow-up. Routine laboratory indicators of disease activity, including C-reactive protein levels, were collected. The different lines of immunosuppressive agents (DMARDs) were studied separately, considering azathioprine, mycophenolate mofetil, leflunomide, methotrexate, and cyclophosphamide. For biological-targeting treatments, each line of various biologics was analysed separately for each patient, including toiclizumab, infliximab, etanercept, adalimumab, certolizumab, and golimumab. This study included 209 patients with TA, with a median age at diagnosis of 29 years (an age range of 7–62), and 186 (89%) females.

RESULTS

According to Numano classification, 20 patients (10%) were of Type I, 68 (33%) Type II, 14 (7%) Type III, 8 (4%) IV, and 90 (44%) Type V. Among the 209 patients with TA, 291 lines of biological-targeting treatments were used during the median 36 months (<1–14 years) follow-up, after a median number of DMARDS of 1 (0–4). Patients with TA received either TNF-α antagonists (n=132 [63%] with 172 lines: infliximab [n=109], adalimumab [n=45], golimumab [n=8], certolizumab [n=6], and etanercept [n=5]), or tocilizumab (n=77 [37%] with 121 lines: intravenous and subcutaneous in 95 [79%] and 26 [21%] cases, respectively), as first biotherapy line. Indications for biological-targeting treatment were insufficient response and/or intolerance to DMARDS in 175 (84%) and first line therapy to active TA in 33 (16%) cases.

Biological-targeting treatments duration was 18.0 months (<1.0 month to 14 years), with a median of 24.0 months (<1.0 month to 14.0 years) for TNF-α antagonists versus 13.0 months

(<1.0 month to 8.8 years) for tocilizumab. The median follow-up was shorter for patients on tocilizumab as first line (30.0 months [2.6 months to 8.7 years]) than for TNF-α antagonists (42.0 months [<1.0 month to 14.5 years]; p=0.0001), respectively. A total of 143 patients received TNF-α antagonists at least once, including first line: 121 (85%) patients switched for this type of treatment once, 16 (11%) patients twice, one (3%) patients three times, and one (<1%) patient for five lines. When considering switches after the first line, a total of 33 patients switched for TNF-α antagonists at least once, subsequently to a first line: 25 (85%) patients switched for TNF blocking agents once, seven (11%) patients twice, and one (<1%) patient for four lines. In comparison to the baseline, the 6 months rates of vascular signs, constitutional signs, radiological activity, National Institutes of Health (NIH) stroke scales, C-reactive protein levels, and prednisone amounts significantly decreased both on TNF-α antagonists and tocilizumab. At 6 months, the clinical and radiological activities and prednisone daily amounts were not significantly different. A complete response (NIH <2 with less than 10 mg/day of prednisone) to biological-targeting treatments at 6 months was evidenced in 101/152 patients (66%) on TNF-α antagonists and 75/107 (70%) patients on tocilizumab. In multivariate, analysis, age ≥30 years (odds ratio: 2.09 [1.09; 3.99]) was associated with complete response, whereas vascular signs (0.26 [0.1;0.65]), baseline prednisone ≥20 mg/day (0.51 [0.28;0.93]) were negatively associated with complete response.

CONCLUSION

In conclusion, the authors conducted the largest study to assess the long-term efficacy of TNF-α inhibitors and tocilizumab in patients with TA. TNF-α inhibitors and tocilizumab seem to have equivalent efficacy and tolerance. However, prospective, large, and randomised studies are necessary to further define the induction and the maintenance therapies in TA. A multi-centre, randomised, prospective trial evaluating the efficacy and safety of infliximab to tocilizumab in refractory or relapsing Takayasu Arteritis (INTOReTAK) is ongoing.[3] ■

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RESOLVE-1, a Phase III Trial of Lenabasum for the Treatment of Diffuse Cutaneous Systemic Sclerosis

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Disclosure: Constantine, Dgetluck, and White are employees of Corbus Pharmaceuticals. All other authors were investigators in RESOLVE-1.

Keywords: American College of Rheumatology composite response index in systemic sclerosis (ACR CRISS), diffuse cutaneous systemic sclerosis (dcSSc), lenabasum, modified RSS.

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BACKGROUND AND AIMS

Lenabasum is an oral, non-immunosuppressive, cannabinoid Type 2 receptor agonist that activates resolution of innate immune responses.[1] In animal models of bleomycin-induced skin and lung fibrosis, lenabasum reduced inflammation and fibrosis.[2-4] In a Phase II study in diffuse cutaneous systemic sclerosis (dcSSc), lenabasum was safe and well-tolerated, and was associated with greater improvement in the American College of Rheumatology composite response index in systemic sclerosis (ACR CRISS) score at Week 16 than treatment with placebo.[5]

RESOLVE-1 was a Phase III study to further test efficacy and safety of lenabasum in adults with dcSSc ≥6 years duration. Background immunosuppressive therapies (bIST) were allowed if doses were stable for ≥8 weeks before screening, to reflect current standard-of-care practice of treating early dcSSc with IST. The primary efficacy end-point was the ACR CRISS score at Week 52,[6] comparing lenabasum 20 mg and placebo groups.

MATERIALS AND METHODS

From 76 sites in North America, Europe, and Asia, 375 subjects were randomised 1:1:1 to lenabasum 20 mg, 5 mg, or placebo, all twice daily. Subjects in the three groups had similar demographic and baseline disease characteristics, with moderate to severe disease overall. Mean disease duration was approximately 32 months, and modified Rodnan skin score was approximately 22 in each group. Subjects were heavily treated with bIST: 84% on any bIST; 51% on monotherapy bIST; 33% on combination bIST; and 51% on mycophenolate mofetil (MMF).

Table 1: Primary and secondary efficacy outcomes.

Outcome	Lenabasum 20 mg BID N=100	Lenabasum 5 mg BID N=113	Placebo BID N=115
Primary			
ACR CRISS step 1=0	n=1, 1 ILD	n=4, 1 CHF, 3 ILD	n=4, 1 renal crisis, 3 ILD
ACR CRISS score, median (IQR)	0.8880 (0.9360)	0.8270 (0.9180)	0.8870 (0.0710, 0.9990)
p value - ranked Score, MMRM	0.4972	0.3486	
Secondary			
Change in mRSS, mean (SD)	-6.7 (6.59)	-7.1 (6.24)	-9.1 (7.72)
Change in HAQ-DI, mean (SD)	-0.133 (0.4363)	-0.060 (0.3917)	-0.127 (0.4677)
Change in FVC, %, L, mean (SD)	-1.602 (6.9106)	-2.248 (6.2099)	-0.993 (8.6840)

Improvement in the placebo group far exceeded expectations based on literature and expert opinions, and the authors were unable to discern treatment effect from the placebo effect.

mITT population: missing visits or the ACR CRISS score core items due to COVID-19 were imputed using LOCF. For other missing data for any core items, imputer used MCMC multiple imputation technique prior to calculating the score, but missing visits were not imputed.

Combined inference statistics: each imputation was analysed by MMRM on the ranked ACR CRISS score with region, disease duration, baseline mycophenolate use, visit, treatment, and treatment-by-visit interaction as the fixed effects and baseline mRSS as a covariate. Secondary outcomes were similarly analysed but using MMRM without a ranked score.

ACR CRISS: the American College of Rheumatology composite response index in systemic sclerosis; BID: twice daily; CHF: congestive heart failure; FVC: forced vital capacity; HAQ-DI: health assessment questionnaire-disability index; ILD: interstitial lung disease; IQR: interquartile range; LOCF: last observation carried forward; MCMC: Markov chain Monte Carlo; mITT: modified intent-to-treat; MMRM: mixed model repeated measures; SD: standard deviation.

RESULTS

The ACR CRISS score at Week 52 was not significantly different between lenabasum 20 mg and placebo groups (Table 1).

Indeed, all three groups had median ACR CRISS scores >0.82, likely speaking to the efficacy of bIST and the ceiling effect of ACR CRISS score. Secondary outcomes showed no significant advantage to treatment with lenabasum. Modified Rodnan skin score improved in all three groups, with mean improvements of 7–9 points at Week 52.

In pre-specified analyses, MMF was found to have a significant effect on ACR CRISS score and certain secondary efficacy end-points, including change in forced vital capacity (FVC). In post hoc analyses, effects of MMF on the ACR CRISS score and change in FVC were more pronounced when treatment duration was shorter at study entry. In other post hoc analyses, subjects on established bIST (≥2 years treatment duration) who received lenabasum 20 mg had stable FVC, whereas those treated with placebo experienced a decline, a difference that was nominally statistically significant.

Lenabasum-treated subjects had numerically fewer serious and severe adverse events than subjects treated with placebo. Adverse events that were more common in lenabasum-treated subjects included dizziness, headache, dry mouth, and somnolence, none of which were serious. Neutropenia, opportunistic infections, and malignancies occurred with similar frequencies in lenabasum and placebo-treated groups, consistent with lenabasum not being immunosuppressive.

CONCLUSION

In conclusion, this study did not demonstrate efficacy for lenabasum in subjects with dcSSc who were receiving standard treatments including

substantial immunosuppressive therapies. Of note, the ACR CRISS scores in all groups far exceeded what was expected, suggesting a possible ceiling effect of that outcome measure in trials that allow bIST. Mycophenolate treatment significantly affected the results, with greater improvement seen in subjects who received MMF. That effect was less apparent in those whose treatment duration with MMF was >2 years at baseline. The suggestion that lenabasum may afford less decline in patients on stable bIST will require confirmation and additional studies. ■

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Epidemiology, Predictors of Mortality and Role of Prophylaxis for Pneumocystis jiroveci Pneumonia Among Patients with Rheumatic Diseases: A Territory-Wide Study

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Keywords: Epidemiology, infection, rheumatology.

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BACKGROUND AND AIMS

Pneumocystis jiroveci pneumonia (PJP) is an opportunistic infection affecting immunocompromised individuals. Its importance in patients without HIV has increased over the past decades due to the expanding armamentarium in immunosuppressive and chemotherapeutic therapies.[1] Given its high mortality rate in non-HIV patients, PJP prophylaxis is commonly prescribed in many immunocompromising conditions and various guidelines have been established in oncology, bone marrow, and solid organ transplant.[2-4] However, evidence regarding the burden of PJP and effectiveness of prophylaxis among patients with rheumatic symptoms remains limited. Epidemiological studies and guidelines for PJP prophylaxis in patients with rheumatic diseases are urgently needed. The objective of this study was to delineate the epidemiology, predictors of mortality, and efficacy of PJP prophylaxis among patients with rheumatic symptoms.

MATERIALS AND METHODS

The authors performed an observational, longitudinal cohort study based on data retrieved from the territory-wide electronic healthcare database (Clinical Data Analysis and Reporting System) of the Hospital Authority (HA).

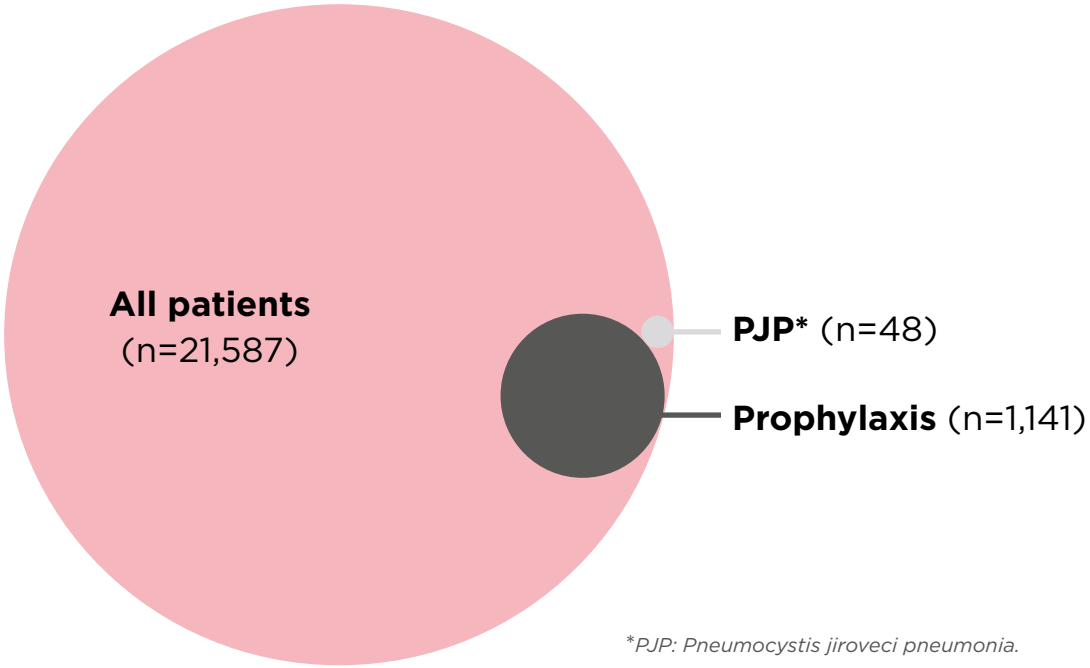

Figure 1: Proportional Venn diagram showing prevalence of pneumocystis jiroveci pneumonia and prophylaxis among patients with rheumatic disease.

HA is the sole public-funded healthcare provider in Hong Kong and covers over 90% of secondary and tertiary care of the 7 million population. All patients with a diagnosis of anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), immune-mediated myositis (IMM), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), or spondyloarthritis (SpA) between 2015–2019 were included. Rheumatic diagnoses were defined based on diagnosis code using the International Classification of Diseases, Ninth Revision. Clinical information including patients' demographics, medication prescriptions, blood tests, and mortality were recorded. Prevalence, prophylaxis, and mortality of PJP were calculated. Number needed to treat analysis was performed. Association analysis was performed to identify predictors of PJP-related mortality.

RESULTS

Over the period of 2015–2019, a total of 21,587 patients were included (54% RA, 25% SLE, 13% SpA, 5% IMM, 2% AAV, and 1% SSc). The majority of the patients were female (73.0%), and the mean age was 58±17.4 years. PJP prophylaxis was prescribed in 1,141 (5.3%) patients. PJP occurred in 48 (0.2%) patients. No patients who developed PJP received prophylaxis prior to infection (Figure 1).

The incidence of PJP was highest among patients with SSc, AAV, and IMM. The frequency of PJP prophylaxis prescribed based on physician's discretion was also highest among patients with SSc, AAV, and IMM. Within these diseases, the majority of PJP occurred while patients were on glucocorticoids at daily prednisolone-equivalent doses of 15 mg/day or above. Using the number needed to harm of 135 for every severe adverse reaction as reference,[5] PJP prophylaxis was effective in SSc, AAV, and IIM with number needed to treat analysis being 36, 48, and 114, respectively.

Overall, PJP has a mortality rate of 39.6%. In univariate analysis, lymphopenia and glucocorticoid dose at time of PJP diagnosis were associated with PJP-related mortality. In multivariate analysis, glucocorticoid dose at time of PJP alone was independently associated with PJP-related mortality (odds ratio: 1.09; 95% confidence interval: 1.02–1.64, p=0.02).

CONCLUSION

PJP is an uncommon but important infection among patients with rheumatic symptoms. PJP

is associated with high mortality. Prophylaxis against PJP is effective and should be considered in patients with SSc, AAV, and IMM, especially those receiving glucocorticoid doses above P15. Glucocorticoid dose is independently associated with PJP-related mortality. ■

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Ultrasound Biomarker Tenosynovitis Predicts Arthritis Development in a Population at Risk of Rheumatoid Arthritis

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Keywords: Anti-citrullinated protein antibody (ACPA), biomarkers, musculoskeletal, musculoskeletal ultrasound (MSUS), rheumatoid arthritis.

Citation: EMJ Rheumatol. 2021;8[1]:64-65. Abstract Review No. AR6.

BACKGROUND AND AIMS

Musculoskeletal ultrasound (MSUS) biomarkers may have an important role to play in the evaluation of individuals with musculoskeletal complaints who are anti-citrullinated protein antibody (ACPA)-positive who are at risk of developing rheumatoid arthritis. The authors aimed to identify which ultrasound markers could predict arthritis development.

MATERIALS AND METHODS

Individuals with musculoskeletal complaints with a positive anti-cyclic citrullinated peptide test were referred to the rheumatology department for a detailed clinical (68 joint count) and MSUS examination of the hands, feet, and any other symptomatic joints. Only those without clinical and MSUS-detected arthritis were included in the Risk RA prospective cohort and followed-up over 3 years or until arthritis onset. Using European League Against Rheumatism (EULAR)–Outcome Measures in Rheumatology (OMERACT) guidelines, MSUS markers for synovial hypertrophy and hyperaemia (Doppler signalling) were documented for each visit. Finger and wrist tendons were screened for any signs of tenosynovitis, and around bursal cavities of feet and symptomatic joints for bursitis. Association of MSUS biomarkers with arthritis development was tested (comparing proportions) using chi-square or Fisher's exact tests.

RESULTS

From January 2014 to October 2019, 287 individuals were included in the study (78% female; 35% rheumatoid-factor-positive; median age: 48 years; interquartile range: 37–56 years). Within a median of 38 months (interquartile range: 1–72 months) since recruitment, 83 individuals (29%) developed an arthritis diagnosis. Prior to obtaining any diagnosis, 33% (94/287) had at least one type of MSUS modification (tenosynovitis, bursitis, synovial hypertrophy, or bone erosions) present, and 55% of those with any ultrasound changes developed arthritis compared with 16% of those with absence of any changes who developed arthritis (p<0.001).

Out of the 287 individuals, 22% (63/287) had ultrasound-detected tenosynovitis and 57% (36/63) of those with tenosynovitis developed arthritis compared with 21% (47/224) with the absence of tenosynovitis that developed arthritis (odds ratio: 5.02; 95% confidence interval: 2.77–9.09; p<0.001). Moreover, 8% (24/287) had ultrasound-detected bursitis and 42% (10/24) of those with bursitis developed arthritis, compared with 28% (73/263) of those with absence of bursitis that developed arthritis (p=0.15). Synovial hypertrophy was noted in 11% (31/287), and 55% (17/31) with synovial hypertrophy developed arthritis compared with 26% (66/256) of those with absence of synovial hypertrophy that developed arthritis (p<0.001). Furthermore, 5% (15/287) had bone surface erosions present and 53% (8/15) of those with erosions developed arthritis, compared with 28% (75/272) of those with absence of erosions that developed arthritis (p=0.03).

CONCLUSION

There appeared to be a trend that the ACPA-positive individuals with musculoskeletal complaints were at high risk where any subclinical minimal ultrasound changes were noted, and that the presence of tenosynovitis at baseline alone was highly predictive of arthritis development. ■

Can Biomarkers Predict Successful Tapering of Conventional Synthetic Disease-Modifying Anti-rheumatic Drugs in Patients with Rheumatoid Arthritis Achieving Stable Clinical Remission?

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Keywords: Conventional synthetic disease modifying anti-rheumatic drugs (cs-DMARDs), rheumatoid arthritis (RA), remission, tapering, T cells, ultrasound (US).

Citation: Rheumatol. 2021;8(1):65–67. Abstract Review No. AR7.

BACKGROUND AND AIMS

It is now accepted that sustained remission is the key treatment goal for rheumatoid arthritis (RA). The availability of biologic therapies and the use of targeted treatment strategies has led to increasing numbers of patients achieving remission; however, specific guidance for the

management of patients with RA in sustained clinical remission, treated with conventional synthetic disease-modifying anti-rheumatic drugs (cs-DMARDs), is lacking.[1-3] This raises concerns for over-treatment in asymptomatic patients. Tapering of treatment is encouraged, although there are no validated biomarkers predicting sustained remission.[4,5] As such, there is an unmet need for predictors of sustained remission for tapering cs-DMARDs, which can be used in clinical practice.

The authors conducted a prospective observational study of two treatment strategies for patients with RA in stable remission. The primary objective was to assess the rate of sustained remission after 12 months, without flare in patients who were offered either structured cs-DMARD tapering or continued therapy. Secondary objectives were to determine baseline predictors of sustained remission following tapering and to develop a predictive model to help aid risk stratification of patients for tapering in clinical practice.

MATERIALS AND METHODS

Patients with RA in clinical remission (Disease Activity Score 28 for Rheumatoid Arthritis with C-reactive protein, [3v-DAS28CRP] <2.6) for ≥6 months on stable cs-DMARD therapy were sequentially recruited from a National Health Service (NHS), UK remission clinic. Patients were offered structured tapering, with 117 accepting tapering and 83 continuing therapy. Clinical, ultrasound (US), immunological (T-cell subsets), and patient-reported outcome (PRO) data were collected. The primary endpoint was the proportion of patients in each group in sustained remission without relapse after 12 months. Flare was defined as loss of DAS28 remission or evidence of at least one new clinically swollen joint. Logistic regression analyses were performed to identify predictors of sustained remission.

RESULTS

Two hundred patients fulfilled the inclusion criteria. No difference in baseline drug regimens (mono- versus combination therapy) was seen

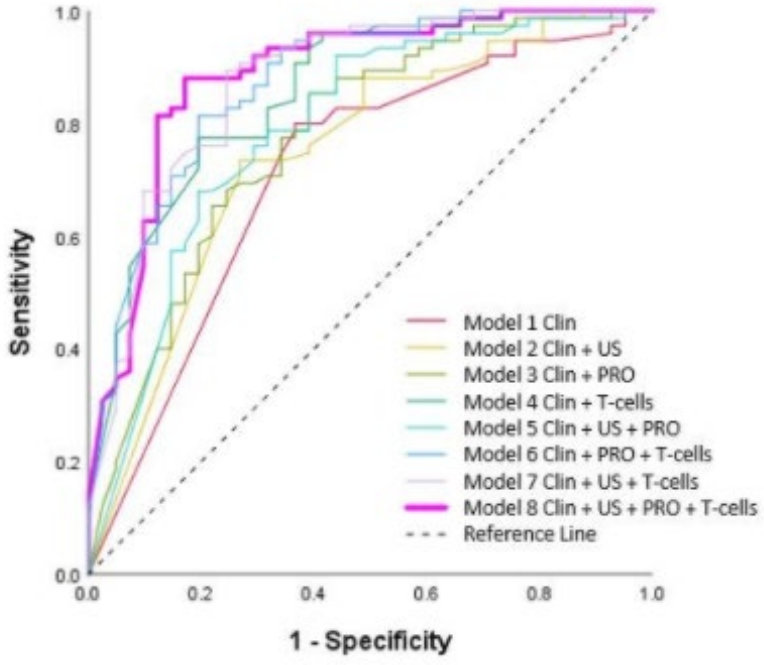

Figure 1: AUROC Models 1–8.
Clin: Clinical; PRO: patient-reported outcome; US: ultrasound.

between the two groups. Male sex (p=0.036) and longer length of remission (p=0.015) were associated with the patient's decision to taper, although not significantly after correction for multiple testing. The tapering group demonstrated lower levels of inflammation-related T-cells (IRC; p=0.001), inflammatory markers, and joint counts. No significant difference between groups was observed for PROs, although there was a trend towards lower PROs in the tapering group.

Of those who tapered, 64% remained in clinical remission after 12 months compared with 80% (p=0.018) of patients on stable therapy. In the tapering group, higher CRP, tender joint count, percentage of IRC, and higher PROs were associated with flare (all p<0.05), with a trend for higher total power doppler score on US (p=0.066). A multi-variable model (using clinical, US, PRO, and T-cell subset variables) predicting sustained remission (Figure 1) retained Rheumatoid Arthritis Quality of Life score (RAQoL), total power doppler score, and percentage IRC (85% accuracy; area under the curve of the receiver operating characteristic [AUROC]: 0.893; p<0.0001). A reference model using clinical variables only (as would be available in clinical practice) demonstrated only 69% accuracy (AUROC: 0.725). Other models, including combinations of two or three variables, demonstrated accuracies between 72–84% (Figure 1). In the non-tapering group, higher CRP, erythrocyte sedimentation rate, swollen joint count, and shorter disease duration (all p<0.05) were associated with flare, with no parameter able to predict sustained remission.

CONCLUSION

The combination of clinical, PRO, US, and T-cell parameters demonstrated added value for predicting sustained remission compared with clinical parameters alone in the tapering group. These data could inform best tapering practice. ■

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Bidirectional Relationship Between Periodontitis and Osteoarthritis in a Population-Based Cohort Study Over 15-years Follow-up

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Keywords: Bidirectional relationship, cohort study, osteoarthritis (OA), periodontitis.

Citation: EMJ Rheumatol. 2021;8[1]:68 Abstract Review No. AR8.

BACKGROUND AND AIMS

Osteoarthritis (OA) has been proposed to result from complement-mediated inflammatory cascades; on the other hand, periodontal disease (PD) has been shown to trigger systemic inflammation through complement-mediated pathways.

MATERIALS AND METHODS

In this population-based cohort study, the authors determined the relationship between OA and PD through 144,788 patients with PD and 144,788 propensity score-matched controls without previous history of PD. Cox proportional hazard regression was used to derive the hazard ratios (HRs) of OA. Survival analysis was used to estimate the time-dependent effect of PD on risk of OA. Age and sex were stratified in a subgroup analysis. A parallel case-control analysis was conducted to investigate whether the relationship between OA and PD was bidirectional through estimating the association between PD and history of OA.

RESULTS

Patients with PD were associated with higher risk of OA (HR: 1.15; 95% confidence interval [CI]: 1.12–1.17; p<0.001) and severe OA that required total knee replacement or total hip replacement (TKR/THR; HR: 1.12; 95% CI: 1.03–1.21; p<0.01) than controls; this association was time-dependent (log-rank test p<0.01). The effect of PD on OA was significant in both sexes and patients aged >30 years (p<0.001). Females (HR: 1.27; 95% CI: 1.13–1.42; p<0.001) and patients aged >51 years (HR: 1.21; 95% CI: 1.10–1.33; p<0.001) with PD were predisposed to severe OA that required TKR/THR. Also, patients with PD were associated with a history of OA (OR: 1.11; 95% CI: 1.06–1.17; p<0.001).

CONCLUSION

In conclusion, these findings support a bidirectional relationship between OA and PD. Patients with PD had a higher risk of OA, including severe OA requiring TKR/THR; moreover, PD may develop following OA. Regular follow-ups for patients with either PD or OA are recommended based on the clinical relevance of this real-world study. ■

VIEW MORE ABSTRACTS ONLINE ←

Congress Interviews

Joan Bathon and Ricardo Ferreira spoke to EMJ about their education, career, and goals, and their roles at the European Alliance of Associations for Rheumatology (EULAR).

Featuring: Joan Bathon and Ricardo Ferreira.

Joan Bathon

Member of the EULAR Scientific Programme Committee; Director of the Division of Rheumatology at New York-Presbyterian Hospital/Columbia University Irving Medical Center, New York, USA

Q1 With your numerous years of experience as a rheumatologist, what initially sparked your interest to pursue a career in this field and motivated you to continue researching?

My first encounter with autoimmunity was in an immunology course in college, during which I learned about systemic lupus erythematosus. The concept that the human immune system could make antibodies against its own cellular and molecular components was fascinating to me. In the latter 2 years of medical school, when we were able to choose electives, I decided to explore this interest more deeply by choosing an elective in rheumatology. The range of illnesses and their unusual and distinctive presentations was more interesting and exciting than I could have imagined. I decided then and there to pursue subspecialty training in rheumatology after an internal medicine residency. During residency, I also found infectious diseases to be extremely interesting, but rheumatology still won out. I was thrilled to be accepted at Johns Hopkins University (Baltimore, Maryland, USA) for my rheumatology training and there was exposed to a breadth and depth of research that I had not experienced previously. I was smitten, especially with trying to understand causality and development of more effective treatments for rheumatoid arthritis. So, that was the beginning of a long career in the field.

Q2 Do you think there are any misconceptions about your speciality?

Yes, absolutely. There is still the very strong perception that we are musculoskeletal doctors like orthopaedists, but without the surgical component. This misconception is understandable because many of our diseases

have an inflammatory arthritis component. Since arthritis is painful, this is often the symptom that initially brings the patient to our attention. But, while many medical specialties are focussed on a single organ like the heart or the kidney or the liver; autoimmune rheumatic diseases are generally multi-organ illnesses. The best example is lupus, which can affect the brain, lungs, heart, skin, kidneys, blood vessels, and more. Moreover, our diseases involve specific patterns of organ involvement that are nuanced and subtle at times. So, explaining autoimmune disease is a little complicated. Getting the message across that we treat illnesses that affect multiple organs characterised by a dysregulated immune system can be challenging, especially because we also do treat conditions that are joint specific (e.g., gout). However, our professional organisations (the EULAR, the American College of Rheumatology [ACR], and others) are really skilled at crafting those messages for the public.

"I was smitten, especially with trying to understand causality and development of more effective treatments for rheumatoid arthritis. So, that was the beginning of a long career in the field."

Q3 The New York-Presbyterian Hospital/Columbia University Irving Medical Center is thought of as one of the top departments in the USA; what do you think other university hospitals could learn from the approach taken there?

Like other top academic Rheumatology programmes, we have recruited or developed a nationally/internationally recognised faculty, each of whom specialises in a particular autoimmune rheumatic disease and contributes new knowledge to the field through research. This research may be clinical (defining disease characteristics or presentation, biomarkers, outcomes) or basic/translational (understanding mechanisms of disease in the laboratory). In some situations, a clinical and a basic/translational investigator are paired and collaborate in the study of their disease of interest. These collaborative approaches within a single disease have facilitated the establishment of dedicated clinical programmes in each major autoimmune rheumatic disease, such as a Scleroderma Center, Lupus Center, Inflammatory Arthritis Center, and so on. The patient who attends an appointment in one of these centres knows they are seeing a

top expert in their disease and who, in turn, has assembled experts in other specialties where necessary to address lung-, cardiac-, kidney-specific complications. So, the patient receives a comprehensive multi-specialty evaluation initially, as well as long term management by a team of top experts in their disease.

Q4 You currently have more than 167 international publications to your name for your research in rheumatology. What do you believe to be the current gaps in literature and what topics merit greater attention?

For the most part, we still do not understand what truly causes our diseases. Much progress has been made on the genetic side, identifying genes that put patients at higher risk for developing an autoimmune rheumatic disease. But genes are generally not enough, in and of themselves, to cause disease but rather require a trigger. We still do not understand what actually triggers our diseases, whether it is an infection, an environmental insult, or other stimulus. We have learned that smoking, for example, is a very significant risk factor for rheumatoid arthritis, especially when combined with genetic predisposition, but in general we have only brushed the surface on identifying critical environmental and infectious triggers. We also now understand that these illnesses have a long asymptomatic phase, during which the immune system is gearing up like an iceberg forming under the surface. Eventually that iceberg rises above the surface and the patient develops symptoms. But we need a better way to identify those asymptomatic individuals during this process so we can intervene while they are still asymptomatic and healthy, to avert the progression to a clinical disease. While most autoimmune rheumatic diseases are characterised by 'out of control' inflammation that must be quelled, several also have a significant fibrotic component (e.g., scleroderma). We particularly do not understand the pathogenesis of this fibrosis and how to prevent it from worsening. While there are some advances in this field which have led to two new U.S. Food and Drug Administration (FDA)-approved medications, the effects of these medications are relatively modest, and much more investigative work is needed. There is still a lot to learn to improve the lives of our patients!

Q5 Since your appointment to Director of the Division of Rheumatology at New York-Presbyterian Hospital/Columbia University Medical Center, what has been your proudest achievement?

Rheumatology at Columbia University has a long and distinguished history. Columbia was the site of the first clinical and research unit dedicated to rheumatic diseases in the USA, the site of the discovery of rheumatoid factor and its link to rheumatoid arthritis, seminal work in the role of immune complexes in lupus, in defining the functions of CD4, CD8, and discovery of CD40L, and the discovery of the HLA-DR 'shared epitope' that conveys the strongest risk for rheumatoid arthritis, and many others. However, when I took over 10 years ago, the Division had contracted to a small, albeit outstanding, clinical division and with only one researcher (a giant in the field: Robert Winchester). I urgently needed to re-build the clinical division but did so first with funded clinical researchers who would build clinical and clinical research programmes in their respective diseases. This would then lay the foundation for attracting basic/translational researchers who study disease mechanisms but need to collaborate with clinical researchers to obtain blood or tissue samples from patients with their disease of interest. This strategy has been successful. We have gone from five faculty members to 15 and are still growing, and our research budget has increased 12-fold. We now have dedicated thriving research programmes in rheumatoid arthritis and juvenile idiopathic arthritis, lupus, scleroderma, spondyloarthropathy, psoriatic arthritis, and immune events related to checkpoint therapy. We still have some gaps to fill, so the work is always ongoing.

Q6 How much of an impact do you believe the EULAR congress has, both directly on rheumatologists and indirectly on patients?

The EULAR congress has a tremendous impact on both groups. From the rheumatologist's perspective, the annual congress is the key mechanism in Europe and beyond for annual clinical education and updates, presentation of novel research findings, enabling networking among clinicians and researchers, and as a platform for the development of guidelines

and recommendations in the field. Its value is immeasurable. For patients, it is a mechanism to bring the voices and now actual physical presence of patients to the table in the discussion of management and treatment of the rheumatic diseases, as well as in cutting edge research. Their voices have broadened our views as rheumatologists in such a meaningful way. EULAR was a real leader in patient engagement before many other organisations had even considered it.

Q7 What are the most significant changes you have seen in the field of rheumatology during your time working in this discipline?

Without a doubt, it has been the progress in the treatment of rheumatoid arthritis. Except for the use of rituximab for lymphoma, advances in the treatment of rheumatoid arthritis in the late 1990s and early 2000s led the medical field in the development of targeted therapies, both biologic and synthetic. Since then the field has exploded with numerous targeted therapies now approved not only for a broader array of autoimmune diseases, but also for cancer, kidney disease, multiple sclerosis, inflammatory bowel disease, and others. While we still see some people with rheumatoid arthritis who have difficult to control disease despite these advances, by and large patients are experiencing remarkably better quality of life and better work productivity than they had prior to 2000. We are seeing similar trends in people with psoriatic arthritis, spondylitis, and vasculitis. Improvements in the management of lupus and scleroderma and myositis have been more incremental but still on a positive trajectory. Ultimately, we would like to cure disease not just suppress it. This is where therapeutic efforts and discovery are still much needed.

Q8 How has EULAR adapted to the 'new normal' of virtual congress and online learning?

Rapidly and effectively. EULAR had only 2 months in the spring of 2020 to pivot from a face-to-face conference, that had been in the planning for over a year, to a completely online conference in June 2020. The contents had to be scaled back but it was nonetheless very effective, and members were much relieved to see each other during this very stressful first wave of COVID. This year the EULAR conference was back to its full robust agenda and went very smoothly. My hat is off to all of those in the EULAR organisation who worked tirelessly to bring about this wonderful meeting. Unfortunately, it was harder for us 'across the pond' to join the live meetings in real time due to the significant time difference. But the enduring nature of the material allows any registrant to catch up on the recorded sessions in their own time zone. I can say that the content this year is as outstanding as ever. ■

Ricardo Ferreira

Chair of the EULAR Committee of Health Professionals in Rheumatology; Clinical Research Nurse and Study Coordinator, Rheumatology Department, Centro Hospitalar e Universitário de Coimbra,Portugal

Q1 You recently co-authored an article on treatment targets in rheumatoid arthritis. Could you please share any emerging evidence on the need to redefine such targets in patients with rheumatic diseases?

The dual-target strategy is still being developed and more research is needed, especially defining the second target's assessment. As a reminder, this proposal aims at fostering person-centred care and reducing the burden of the disease by using two complementary targets: one focussed on the disease process (the biological target) and the other focussed on symptoms and impact (the impact target).[1] We proposed that the Patient Global Assessment (PGA) of disease activity should not be included in the definition of the biological target but instead replaced by more meaningful measures included in a different target of equal importance. Several papers have presented compelling evidence to dropping out the PGA, but this has been the controversial part of the proposal. Our most recent publication shows that a high PGA in patients with rheumatoid arthritis otherwise in remission do not reflect subclinical inflammation.[2] This result further supports that PGA is more a measure of symptom severity and disease impact than a true reflection of disease activity. We now need to obtain a broader consensus on how this may be applicable in clinical practice with the input of the different stakeholders. I do believe that this proposal will also prompt a better interdisciplinary collaboration in rheumatology.

Q2 As the Chair of the EULAR Health Professionals in Rheumatology (HPR) Representation Committee, could you explain what this position entails and how it contributes to the success of EULAR?

As Chair of the EULAR HPR committee, together with the Past-Chair or Chair-Elect, I am asked to initiate, drive, and manage the projects under the HPR committee umbrella. These projects include the educational offerings (e.g., online and face-to-face courses), scientific outputs (e.g., clinical practice recommendations), knowledge translation activities (e.g., assessment and promotion of implementation activities), or awareness and advocacy actions, desirably in close co-operation with other EULAR committees (e.g., PARE) or organisations (e.g., American Rheumatology Professionals). HPR is composed of three sub-committees (Educational, Scientific, and Knowledge Translation) and has a maximum of 25 members. The committee meets at least twice a year to discuss the interests and projects of the HPR as well as EULAR business.

The Chair of the committee, together with the HPR Vice-President, is also an inherent member of the scientific committee of the EULAR annual congress, which is another challenging but equally rewarding task. The contribution to the success of EULAR is also provided through the active participation and voting on the EULAR Council Meetings and smaller meetings with the other committee's chairs, to bear our collective expertise as a 'think tank' for EULAR and to reflect on long term strategy.

Q3 You were appointed Chair of the EULAR HPR last year when academic learning and meetings were made virtual in response to the pandemic. What has been your proudest achievement over this past year?

Indeed, after being appointed as Chair I was only able to participate in one face-to-face meeting of our HPR committee (Lisbon, December 2019) and all other essential meetings, such as the annual congresses, went online. This could have

"The contribution to the success of EULAR is also provided through the active participation and voting on the EULAR Council Meetings and smaller meetings with the other committee's chairs, to bear our collective expertise as a 'think tank' for EULAR and to reflect on long term strategy."

affected the commitment and motivation of committee members, but that was not the case. We were able to adapt and improve in different ways. For instance, after postponing the first HPR post-graduate course, a 2-day interaction in Madrid course with language facilitation (Spanish and Portuguese) for the first day, we changed it into an online interactive course with great success. We implemented some innovative engagement strategies, such as clinical case discussions during the weekdays, in a forum per group, facilitated by mentors, in preparation for the synchronous sessions on Fridays, when the lectures and workshops took place. We had more than 150 applications, from different continents, and with many rheumatologists applying.[3] We were also able to initiate new important projects, namely a task force to develop recommendations for the management of fatigue in people with inflammatory arthritis. However, some of the most important achievements, not only from this but from all committees, was the change in our internal organisation, which required new bylaws, changing the members. Being able to keep all HPR community engaged and active was a proud achievement, considering all the challenges we all have been through.

Q4 How have you developed the skills to perform your role as Chair of this committee? How do you monitor the performance of the organisation?

I have been able to participate actively in all these activities as Chair thanks to the outstanding support from my predecessor, Rikke Helene Moe, and the excellent collaboration we had with the HPR Vice-President, Thea Vliet Vlieland, with monthly meetings and uncountable emails and WhatsApp discussions. We can say that the Chair has a more operational role and the Vice-President more an organisational one, but we work very closely. My previous role as member of the HPR scientific sub-committee for 4 years, the participation in some EULAR task forces and study groups also helped me to develop my skills. I have also made some short educational visits to other rheumatology departments in the Netherlands and France, which allowed me to see how other healthcare systems, and particularly how rheumatology, can be organised, e.g., in terms of multi-disciplinary collaboration, educational, or preventive interventions.

One of my best competences, I believe, is the capacity to observe and liaise to others, and I have watched the way other Chairs manage their committees and took some important advice.

To monitor all the activities, I have the support from the EULAR secretariat, and all documents (including periodic follow-up reports) are stored in an internal cloud, which the Chairs can monitor at all times. But, more importantly, we have strengthened the communication and given more autonomy to the leaders of the three HPR sub-committees. They can have their own meetings and we also meet and communicate quite often.

Q5 What is one of the biggest challenges for the EULAR HPR in their goal to promote multidisciplinary collaboration in the treatment of rheumatic and musculoskeletal diseases in Europe?

EULAR involves, in all its initiatives, people from diverse background professions, different countries, sex balance, always patient representatives, and sometimes other stakeholders. However, despite this collaborative perspective when developing new products, for instance, clinical practice recommendations, their implementation is more difficult and depends a lot on the structure and organisation of countries' healthcare systems. Unfortunately, most of the countries are still centred in a biomedical paradigm, where the physician and the pharmacological treatments are the central

interventions. The success of the healthcare sector is measured by the number of medical consultations, surgeries, length of hospitalisation, and life-time expectancy. However, we all know that other outcomes are also essential, but not considered, such as quality of life, self-efficacy, work productivity (or healthy working years), among others. Healthcare systems who promote the multi-disciplinary teamwork from the onset of the disease process, and not only when drugs are not enough, have much better outcomes. We can look for instance to the Nordic countries and to the osteoarthritis management.

Another important challenge is to promote a balanced development for all the professions represented by this HPR committee, including nurses, physiotherapists, occupational therapists, psychologists, nutritionists, social workers, pharmacists, exercise scientists, among others. In different countries, these professions have specific competencies, educational and legal bases and to promote a European framework to the rheumatology speciality for each of these professions is a true challenge. We have addressed so far only the generic competences,[4] but I believe that in a near future, EULAR HPR will need to liaise with European professional bodies to discuss this consensual speciality framework like the rheumatologists have.

Q6 How much of an impact do you believe the EULAR and EULAR HPR have on both rheumatologists and patients?

EULAR will celebrate its 75th anniversary in 2022 being worldly recognised organisation, which has been adapting through the years. The HPR Committee was officially formed in 1989, and has continuously evolving, having a third sub-committee created in the present year: the knowledge translation. In a similar way the 'patient's committee' had a precursor organisation, the Social Leagues, in 1973, and formalised in 2008 as it is currently known: the PARE committee. Altogether, these EULAR communities made efforts to reduce the impact of rheumatic and musculoskeletal diseases (RMDs) on the individual and society and to improve the social position and the quality of life of people with RMDs in Europe. Naturally, not all health professionals are aware of the important documents and learning opportunities produced by EULAR. This is a very important role of the national associations of rheumatologists, HPR, and patients, to increase this awareness and to promote national capacity to improve RMD access and quality care. We all recognise that language is a barrier and different efforts have been made, such as translations of key messages and lay summaries, among others. Nevertheless, we have plenty examples on how the recommendations produced by EULAR, as well as the educational visits, courses, grants and other services have shaped the organisation of national departments and patient's lives. We also believe that the involvement of 'national champions' in EULAR activities is key to prompt changes.

Q7 Based on your experiences, what advice do you have for rheumatologists in the early days of their careers?

My advice would be in investing time of their education on communication and empathy skills as these are essential in every clinical contact, but indispensable for caring people with chronic diseases. RMDs impact the patient's lives in many ways and we all recognise that pharmacological treatments, despite impressive advances, are not enough to abrogate disease impact. This calls for the importance of a multidisciplinary integrated approach. Asking the support or collaboration from other team members, such as podiatrist, psychologist, nutritionist, occupational therapist, among others, is not a sign of incompetency. On the contrary, evidence states that addressing issues such as depressive symptoms or obesity from early diagnosis and pharmacological intervention will improve the clinical response in terms of disease activity, improving overall quality of life. ■

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Interviews

Christopher Edwards and Karen Walker-Bone spoke to the EMJ about their ongoing passion for rheumatology, the driving forces behind their work, and the effects of COVID-19 on their field in the last year.

Featuring: Christopher Edwards and Karen Walker-Bone.

Christopher Edwards

Professor and Consultant Rheumatologist and Honorary Chair of Clinical Rheumatology; Musculoskeletal Research Unit, NIHR Clinical Research Facility; University Hospital Southampton NHS Foundation Trust, UK

Q1 What do you most enjoy about being a rheumatologist?

I think rheumatology is a great speciality because it's a mixture of all of the medical specialities, and the diseases we look after can affect many different organ systems in many different parts of the body. Some of those are acute and shortlived, some of those are chronic and long-term. You get to understand patients and people over a longer period of time and the reason I became a rheumatologist was [because of] multi-system inflammatory diseases like lupus; they involve different organ systems and sometimes they are complicated, they need judgment, and I found that attractive.

Q2 What skills or attitudes did you have when starting your career, and how do you think they have helped or hindered you as you progressed in the field?

Rheumatology requires all these different skills to pull together information from lots of different places. I think good rheumatologists often have the ability to take information from blood results, from imaging, listening to the patients most importantly and from examining the patient and weighing that altogether. One of the things that I'm really interested in is how you know when you have crossed the threshold that allows you to make a decision; often what a rheumatologist needs to be able to do is weigh up the risk and

the benefit in a complex situation. Maybe this is true for many physicians, but you often need to weigh up situations where the evidence isn't all there, so you try to make a decision with incomplete information to do the best for the person in front of you. That's a challenge, but I think it can be very interesting and rewarding as well and I suppose that's something that never lets up.

"One of the things that I'm really interested in is how you know when you have crossed the threshold that allows you to make a decision; often what a rheumatologist needs to be able to do is weigh up the risk and the benefit in a complex situation."

Q3

Why are the environmental causes of autoimmune rheumatic disease and new therapies for rheumatoid arthritis and lupus a particular interest of yours?

When you have complex diseases, particularly immune and inflammatory diseases, trying to decide what the underlying causes are is really interesting. We know what we are is a mixture of our genes: what we inherit passed down from generations of our ancestors. And of course, the genetics of our immune system is heavily influenced by the infections that were around our ancestors as they were passing through the last few 100,000 years. We needed to have very nasty immune systems to protect us from infection and we have really needed that over the last year with COVID-19. Of course, that immune system gets it wrong sometimes and the environment can 'help' (that's probably the wrong word) to get it wrong. There are some things in the environment that stimulate the immune system to make the immune system more likely to make a mistake and to say 'that joint looks foreign' or 'that bit of tissue doesn't look like it belongs here'. The immune system then attacks. Some of the classic environmental factors include smoking, certain sorts of infection, sunlight exposure for lupus. There are things that happen to us in the environment and other things that are inherent within us and it's that combination that gives the risk of developing one of these illnesses such as lupus.

Q4

Looking back at your career thus far, what has been your proudest achievement?

I think probably some of the biggest achievements have been over the last year for me and maybe that's because it's so recent. I have a few roles: I'm a consultant rheumatologist, but I am also

"The drug developments have also gone hand-in-hand with massive advances in technology, such as in molecular biology which has improved our ability to phenotype a patient more accurately."

an associate director of a National Institutes for Health Research (NIHR) clinical research facility. These are the environments where translational medicine studies are performed. At the start of the pandemic in 2020, and at high speed, many clinical research facilities across the UK, including ours in Southampton, were repurposed to primarily do COVID-19 studies. If I think about proud moments, then standing in the big gymnasium at the University of Southampton in April time last year I remember seeing some of the first Phase I patients going into the Oxford/AstraZeneca vaccine study and hoping it would be effective. I was just impressed by all the brave volunteers and all the dedicated research staff and seeing what they had been able to achieve in such a short time.

It didn't matter that I was a rheumatologist or that one of the nurses usually did respiratory studies, everyone was working flexibly towards a common goal. I think that was the proudest thing. That was amazing to see.

Q5 Over the 20 years you have been practising as a rheumatologist, how have you seen the field change, specifically with regard to advancements in the technology and therapies used? What do you think are the key advantages and disadvantages of this?

Some of the key things are the obvious headline ones, such as the developments in new therapies. I was appointed as a consultant about 20 years ago and that was about the time biological therapies became available to treat rheumatoid arthritis. I was really lucky to be at the Kennedy Institute in London [now University of Oxford, UK] when some of those early studies were being done. These treatments have transformed the lives of many patients and you really see that in very simple things; if you had taken a photo of the waiting room when I was a trainee or a student at King's College London, UK, you would have seen many patients with rheumatoid with damaged and deformed joints using wheelchairs. Therapists spent time making them special knives and forks to use so they could eat for themselves. It's a terrible disease. Now, if you went and took a photo of the clinic in Southampton, which will be the same around the country and around the world, people no longer experience damage like that. For the majority, new therapies have made a massive difference, but it's also more than that. It's the ability to do fantastic research studies, to answer questions about how we should approach the strategy of treatment, treat early, treat to target, keep changing medicines if they don't work, and encouragement of a restlessness to keep altering and trying to improve things if it doesn't work for a patient. The drug developments have also gone hand-inhand with massive advances in technology, such as in molecular biology, which has improved our ability to phenotype a patient more accurately.

Q6 Are there any innovations on the horizon in the field of rheumatic surgery that you believe to be a major breakthrough?

There are certainly more new therapies. We have moved from a situation where we've had biological therapies, large molecules that have to be injected, and we've gone to a situation

where with some of the smaller molecules being developed like the JAK inhibitors, we can give people a tablet to do a similar sort of job.

Then there's stratified and personalised medicine, where we are trying to pick the correct approach for an individual rather than assuming 'one size fits all'. It's trying to give someone a bespoke treatment as opposed to something that's just off the shelf for everybody.

I'm also interested in the effect of chronic inflammation on the brain and how illnesses that cause chronic inflammation have effects on people's mood, on depression and anxiety, and on their cognitive function as well. How quickly and how well people can think is affected and so that link between systemic inflammation and other diseases is fascinating. The brain is like the deep oceans: there are still lots of things we don't understand about it. I think that is one to watch for the in the future.

Q7 One of your current projects includes understanding the treatment of rheumatoid arthritis in the UK. What have been the greatest challenges faced by the NHS and rheumatologists during the COVID-19 pandemic?

I am going to say three things; maybe there are lots more but there are three major things. One is about repurposing what we do and I've mentioned already that in an emergency like this you have to use people's skills to do many different jobs. Many rheumatologists and many rheumatology nurses have had to spend time on COVID-19-related work. It's what we do, and I think most people have been happy to use their medical skill to try to help by working in that environment. But, that was a challenge.

Then there's the challenge of having a group of patients whose immune systems don't work normally who then go on immunosuppressive drugs and initially not understanding how high their risk was of getting bad COVID-19, being hospitalised or dying. How much did they need to shield? Should we continue their immunosuppressive therapies? It turns out a year later that many of the therapies we use don't really increase the risk. Some of them have been used to treat COVID-19, like dexamethasone or the IL-6 inhibitor tocilizumab. With current knowledge we're a bit less worried now and the increased risk of a poor outcome with COVID-19 for patients with rheumatic diseases is more to do with people being older or having other comorbidities.

Then the last thing, and probably the most difficult thing, is that when all of the drama of the last year settles down people will realise that for the last year many patients with disease haven't been diagnosed or haven't received timely care. There are enormous waiting lists building up in hospitals. The challenge now is how people manage that and catch up over the next probably 2 or 3 years. That's a real challenge for people.

Q8 Your contributions to continuing medical education is represented in your role on the European Alliance of Associations for Rheumatology (EULAR) Education Committee. Where can we expect to see the focus of the Education Committee lie in the coming years?

I'm the Chair-Elect of the EULAR education committee; so, from June 2021, I'll be the Chair of the EULAR education committee.

Some of the focus in the last year has been on the challenge of COVID-19 and how it delayed research studies and interrupted lots of educational events, which would normally have been face-to-face events but now are virtual. We have learnt about how you can get the best out of virtual meetings. There needs to be shorter talks and longer for discussion so we can really hear what experts think. If someone is sitting at a computer screen, it can be very hard to sit through a long lecture or a whole meeting. I think some meetings will remain virtual or hybrid and for certain formats it can work very well. Another change is that the EULAR online educational courses are going through a process of being updated to a more modern format. I think people will enjoy this and I would encourage everyone to take a look. We are also working on standards needed to train rheumatologists across Europe. EULAR is committed to providing high-quality educational opportunities that are relevant to rheumatologists across the world. We are always looking for new ideas.

Karen Walker-Bone

Professor and Honorary Consultant in Occupational Rheumatology, University of Southampton; Director, Arthritis Research UK/MRC Versus Arthritis Centre for Musculoskeletal Health and Work, Southampton, UK

Q1 What were the particular experiences or inspirations you had growing up that led you to undertake a degree in medicine?

To be honest, it was just all I ever wanted to do (apparently from the age of 3 years onwards)! Luckily, I found myself being competent at science subjects at school, and everything I did and learned confirmed my enthusiasm for medicine. I was fixated with television programmes about hospitals, doctors, and healthcare and read as many books as I could get my hands on that were about doctors and medicine. My mother was one of six children and my dad one of four. Neither of them went to university (my dad joined the army at 15). There are no doctors in the family and just one of my mum's sisters is a nurse. Having nobody to discuss this with didn't put me off at all; I was the first to go to university!

Q2 Additionally, what experiences during medical school and your doctor training led you to specialise in rheumatology?

I loved every specialty at medical school and after I qualified, I really thought I wanted to do paediatrics until I was unlucky enough to see a child in an intensive therapy unit who was brain dead after meningitis. I thought hard about palliative medicine, but rheumatology just drew me in; the more I did it, the more I liked it. I loved it when the same patient came back to see me over time, and I could find out what difference (if any) my suggestions had made. When I first started, we had only just stared using methotrexate in low doses and many patients were severely disabled with their inflammatory arthritis. We had 18 beds in our ward and people were admitted for bed rest and hydrotherapy or pulses of high-dose steroids intravenously. It was so important to me to talk to them, understand what they wanted, and help them reach their goals if at all possible. Most patients we see now are living much more normal lives, but I have never lost the need to find out what the patient wants and try to help them achieve it.

Q3 Having taken time out in between clinical training to complete a PhD in epidemiology, how do you think your prior clinical experience influenced the way you approached and completed your doctorate?

Interesting. I usually think of it the other way around; in other words, what my PhD brought to my subsequent career. I guess I was already organised, enthusiastic, and passionate and I had a clear idea of how disabling rheumatic and musculoskeletal diseases were and therefore how important it was to do research and make things better. I was also lucky to be able to continue clinical work alongside my PhD, funded by a PhD fellowship from Versus Arthritis (then called Arthritis Research Campaign), and I did a very applied and clinical piece of research. I studied the prevalence and impact of neck and upper limb disorders in 10,000 working-aged adults in different parts of Southampton. In total, we examined 2,000 of them and I personally followed-up 150, so it was a very 'hands on' PhD. Our data remain very highly cited even today.

Q4 Much of your work focuses on the quality of health in the work environment and how we can minimise the impact of musculoskeletal disorders. Could you explain any recent findings within this area and what effects these will have on the future workplace?

The origins of occupational health lay in describing hazards to health in the workplace that were previously undetected (e.g., asbestos and coal dust) and protecting workers. Thankfully, we know much more about these

"Most patients we see now are living much more normal lives, but I have never lost the need to find out what the patient wants and try to help them achieve it."

types of hazards now and we can focus more on prevention and workplace wellbeing. The fact is that we all spend roughly 10 complete years of our lives at work (the only thing we do more of is sleep: on average, for 23 years). Therefore, work needs to be a place where, of course, we are safe but also, we promote wellness and health. Mental ill health and musculoskeletal problems are very, very common even amongst healthy people but these can 'tip over' and become disabling. In both cases, work can cause or make these problems worse, so it is vital that we identify those situations in order to prevent ill health. However, a lot of people will have these conditions and still be at work, so we need to promote wellness in the workplace and enable people to retain their health through a good, supportive working environment. People who are made redundant or fall out of work through ill health suffer far more with debt, stigma, and needing to try and live on welfare benefits. Debt is frightening and makes health (particularly mental health) worse. As our life expectancy has gone up, we need to rethink working lives and workplaces. It may be that people of the future could have two or three careers over their lifetime and come into or out of career breaks for training, education, caring responsibilities, etc. There is no doubt that pensions would be more affordable if we could enable people to work to older ages. Workplaces need to change in the future.

Q5 Do you see foresee the remote working situation as a result of the COVID-19 pandemic having an impact on the relationship between work and musculoskeletal health? How?

That is a good question, and we might need a crystal ball! It could be good or bad. There are benefits in some ways of less time spent commuting, more flexibility of how and when to work, and having the potential to do exercise, stretches, and generally move more at home rather than be tied to a desk at work because everyone else is having lunch at their workstation. However, many people have felt isolated, worked at suboptimal workstations with inadequate equipment, and felt stressed by the use of technology and 'Zoom fatigue' from being on video constantly. How often do we have to watch ourselves whilst we talk to colleagues? Equally, teams do need contact and social interaction beyond work to enable their efficiency and effectiveness. Employers could use all these lessons to be more flexible with work. People can be trusted to get their work done without having to be monitored at their desk. Offering flexibility and choice about how and when people work could enable a lot more participation from older workers and people with health conditions. However, people like some choice and working from home is not for everybody. To sum up, the

"However, a lot of people will have these conditions and still be at work, so we need to promote wellness in the workplace and enable people to retain their health through a good, supportive working environment."

'good' employers will benefit from the learning and will gain loyalty and high productivity by enabling flexibility but there are lots of not very good employers out there.

Q6

In terms of collaboration, what is needed from research institutes, the government, and society to effectively instate cost-effective measures that minimise musculoskeletal disorders in the workplace?

It interests me how different countries do this, and we perhaps need to look more widely. In the UK, healthcare is free to all at the point of delivery (how lucky we are) but that does mean that some less urgent care is more variable in quality and might require waiting on a waiting list. Unfortunately, musculoskeletal care is one of those areas. Physiotherapy, orthopaedic surgery, etc, are all things that can markedly improve pain and function and keep people working but people can fall out of work waiting for their treatment. At present, government does not 'join up' health costs and benefits costs. If the economic argument could be made, then better, quicker musculoskeletal care might well be cost-effective for keeping people at work. In other countries, insurance systems 'kick in' very soon after a worker goes off sick and these companies provide support and rehabilitation to get people working because it saves the insurance company money; they are incentivised to help the worker. We don't have any such system here. Some people have paid sick leave for up to 6 months, some people self-insure or have employers who pay insurance, but many others have limited paid sick leave. This imbalance makes the costs very difficult to track as they are all coming out of different budgets. The individual with a health condition can find themselves stuck out in the cold, losing confidence, deskilling, and becoming anxious and depressed, all of which will hamper their recovery. Importantly, as I said earlier, employers vary and we really could look at some sort of incentives to employers for being 'good' employers: promoting healthy work practices, listening to their staff, supporting healthy lifestyles, and more.

Q7

What aims do you have to spread awareness of and apply your research across the world?

These issues are really a matter of public health. Work and health are inextricably linked. Some countries do this better than we do in the UK, but many others do not. We need to always keep capacity to do this research in the UK because our health and welfare system is fairly unique; something that might work in the USA might not work here because the levers are different. However, some lessons generalise. Workers who are involved actively, listened to, paid adequately, who have optimal working conditions, and who feel as much control as possible over their jobs are generally happier, healthier, and more loyal, with the added bonus of being more productive for their employer.

Q8

With a wealth of experience in teaching and developing modules and materials for medical students, what advice would you give to other university lecturers on how to deliver high-quality education while concurrently delivering inspiration and motivation to newer generations of doctors?

I wouldn't feel at all qualified to give such advice, to be honest. Many others are far better than me. I genuinely love what I do and want to share it with others. I think one's passion comes across to students and that they will 'buy in' with enthusiasm if they hear yours. I always review any lecture before I give it and keep it up to date. Things change all the time and, to be honest, I would be bored myself if I didn't refresh them as I go along. The people who I chose as mentors and role models were those who were enthusiastic and passionate about what they did and that is what I try to be. I learned early that patients are the best teachers, so I use a lot of patient stories, and indeed actual patients, in my teaching when possible. It is the great privilege of being a doctor and delivering medical education.

Management of Pregnancy in Rheumatic Disease

EDITOR'S PICK

The Editor's Pick is the review paper by Maguire et al. Managing patients with rheumatic musculoskeletal disorders (RMD) during pregnancy and the postpartum period is challenging. Disease activity in some RMDs, such as rheumatoid arthritis, improve during the course of pregnancy and in others, such as systemic lupus erythematosus, it worsens. Then there is the issue of drug treatment during pregnancy to maintain remission and the potential undesirable effects on the fetus. This complex subject area is reviewed as well as the current American College of Rheumatology (ACR) guidelines on pregnancy and RMDs.

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Abstract

Managing patients with rheumatic diseases (RMD) during pregnancy and the postpartum period can be a challenge for both rheumatologists and obstetricians. While disease activity during the course of pregnancy varies with regard to the presence of underlying conditions, maintenance of remission from conception through to delivery increases the chances of an uncomplicated pregnancy. A period of remission of at least 6 months prior to conception increases the chance of a successful conception while decreasing the risk of flares during pregnancy. For this reason, discussion of pregnancy in females with RMDs should begin prior to conception with risk stratification and pregnancy planning. This allows for the transfer to pregnancy-compatible medications, disease stabilisation, determination of autoantibody status, and evaluation of end-organ damage. During pregnancy, where possible, disease activity should be monitored with scores modified to allow use in pregnancy. Prompt recognition and treatment of active disease is essential to minimise the risk to the pregnancy. Systemic lupus erythematosus and axial spondyloarthropathy can present diagnostic dilemmas due to overlap of symptoms of disease activity and normal pregnancy. Patients with end-organ involvement, such as systemic lupus erythematosus or systemic sclerosis, face a higher risk of adverse pregnancy outcomes and disease progression. Close monitoring of patients with RMD should be done by both obstetrics and rheumatology, with regular communication between specialties. Medications should be reviewed at each stage of pregnancy to ensure compliance with the current American College of Rheumatology (ACR) guidelines and the adequate treatment of RMDs.

INTRODUCTION

Many patients with rheumatic diseases (RMD) are diagnosed during their childbearing years.[1] Historically, females with RMDs were advised to avoid pregnancy due to potential risk to both mother and fetus.[2] Because of advances in detection of disease activity and therapeutics, this is no longer the case and most females with RMDs can safely become pregnant;[3] however, they may face an increased risk of a number pregnancy-related complications and require closer monitoring during their pregnancy.[4]

Pregnancy with RMD should involve a period of planning between the patient and rheumatologist prior to actively trying to conceive.[5,6] The primary objective in managing a pregnancy is both a healthy mother and child. In order to ensure favourable outcomes, a number of factors, including medication usage, disease activity, and antibody status, must be evaluated and managed (Table 1).[7] Pregnancy planning to risk assess and address these issues allows the rheumatologist to help their patients safely navigate both the pregnancy and postpartum period.

During pregnancy, the female body undergoes a series of significant physiological and hormonal changes, which can affect disease activity.[8] During pregnancy, these patients can pose a challenge to rheumatologists as flares can be confused with complications or physiological changes of pregnancy. Advances in understanding of the disease processes has helped differentiate between these processes. Level of inflammation at the time of conception has been shown to directly impact pregnancy outcome, making control of disease activity essential.[9,10] A number of disease activity scores have been modified for use in pregnancy; however, most are focused around rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), with a considerable paucity of tools for other RMDs.[11] For this reason, close monitoring by both rheumatology and obstetrics is necessary during the course of pregnancy.

SEARCH STRATEGY

For this review, PubMed, Cochrane, and EMBASE were searched for articles related to pregnancy in RMD, with more specific searches for each RMD.[12] Preference was given to more recently published literature to reflect most recent research. Bibliographies of included articles were also searched for additional sources.

Table 1: Factors of rheumatic diseases involved in pregnancy outcome.

Positive impact	Negative impact
Pregnancy planning and counselling	Active disease§
Disease remission*	End-organ damage: • Lupus nephritis • Pulmonary hypertension • Restrictive lung disease
Known autoantibody status	
Medication adherence	
Use of pregnancy-safe medications†	Unplanned pregnancy
Close monitoring of disease activity‡	Unplanned cessation of treatment**
Optimisation of general health	

*Remission of disease for at least 6 months prior to conception and throughout pregnancy.
†Adjusted for each stage of pregnancy.
‡With outcome measures adjusted for pregnancy where possible.
§Both prior to conception and during pregnancy.
**Without consultation with a rheumatologist due to risk of disease activity.

PRIOR TO CONCEPTION

Counselling and Planning

For females with RMDs, pregnancy planning is an essential component of pregnancy in the months prior to conception. The importance of this period of planning and counselling in RMD cannot be understated. Lack of pregnancy planning in the general population has been associated with increased incidence of low birth weight and even neonatal mortality.[13,14] Unplanned pregnancies are also associated with increased rates of smoking, stress, and lack of prenatal care.[15] This is also seen in patients with RMDs but conception is further complicated by risk of active disease and use of medications not compatible with pregnancy.

Recent studies in SLE demonstrated that lack of planning for pregnancy was a significant predictor of adverse pregnancy outcomes.[16]

This issue is correctable with improved patient education and increased physician-led discussion of family planning during rheumatology consultations.[17] Barriers to these conversations discussed in a SLE focus group include busy clinic schedules and difficulty initiating pregnancy conversations.[18] However, this group also highlighted the disconnect in patient and physician risk perception of pregnancy, which could be remedied by open conversations about pregnancy as part of regular rheumatology consultations.

Disease Control

Control of maternal disease during pregnancy is associated with improved pregnancy outcomes and lower risk of fetal complications.[5,9] The importance of disease control begins in the pre-conception stage, as females with active disease are advised to wait for remission prior to actively trying to conceive.[6,7] Patients planning for pregnancy should be in remission for at least 6 months prior to conception.[10] Patients with significant end-organ damage should be counselled on their risk stratification prior to conception.[19] In cases of severe disease, including advanced pulmonary arterial hypertension (PAH), chronic renal impairment Stage IV/V, or in cardiac failure, there is considerable risk of maternal morbidity and mortality. In such cases, individuals should be advised against pregnancy (Table 2).[10,17,20]

Table 2: Relative and absolute contraindications to pregnancy in patients with rheumatic diseases.[12,19,21]

Relative contraindications	Absolute contraindications
Severe SLE flare within the past 6 months*	Advanced pulmonary hypertension
Stroke in the past 6 months	End-stage renal disease
Pulmonary hypertension	Severe cardiac failure
Severe restrictive lung disease	
Moderate to severe cardiac failure	
Severe valvular disease	
CKD stage 4–5	
Uncontrolled hypertension	
Previous early-onset pre-eclampsia or HELLP†	

*Including renal flare.
†Despite therapy with aspirin and heparin.
CKD: chronic kidney disease; HELLP: haemolysis, elevated liver enzymes, and low platelets.

Table 3: Summary of the American College of Rheumatology (ACR) guidelines on medication for rheumatic disease usage during conception, pregnancy, and lactation.[9]

Conception			
Safe to continue	**Conditionally recommend to continue**	**Stop prior to conception**	**Unknown**
Hydroxychloroquine Sulfasalazine Colchicine Azathioprine Certolizumab pegol Cyclosporine Tacrolimus	Prednisolone[a] Cyclosporine NSAIDs Infliximab Etanercept Adalimumab Golimumab Rituximab[b] Anakinra[b] Belimumab[b] Abatacept[b] Tocilizumab[b] Secukinumab[b] Ustekinumab[b]	Methotrexate Leflunomide Mycophenolate mofetil Cyclophosphamide Thalidomide	Tofacitinib Apremilast Baricitinib
Pregnancy			
Safe to continue	**Conditionally recommend to continue**	**Stop prior to conception**	**Unknown**
Hydroxychloroquine Sulfasalazine Colchicine Azathioprine Certolizumab pegol Cyclosporine Tacrolimus	Prednisolone[a] Cyclosporine NSAIDs[c] Infliximab[d] Etanercept[d] Adalimumab[d] Golimumab[d] Cyclophosphamide[e] Rituximab[f]	Methotrexate Leflunomide Mycophenolate mofetil Thalidomide Anakinra[g] Belimumab[g] Abatacept[g] Tocilizumab[g] Secukinumab[g] Ustekinumab[g]	Tofacitinib Apremilast Baricitinib
Lactation			
Hydroxychloroquine Sulfasalazine Colchicine Certolizumab pegol Infliximab Etanercept Adalimumab Golimumab Rituximab	Azathioprine[h] Prednisolone[i] Cyclosporine[h] Tacrolimus[h] NSAIDs[j] Anakinra[k] Belimumab[k] Abatacept[k] Tocilizumab[k] Secukinumab[k] Ustekinumab[k]	Methotrexate[l] Leflunomide Mycophenolate mofetil Cyclophosphamide Thalidomide	Tofacitinib[m] Apremilast[m] Baricitinib[m]

[a]Minimise dose to <20 mg/day with use of alternative pregnancy-compatible immunosuppressant.
[b]Discontinue at conception.
[c]Avoid after 32 weeks to prevent premature closure of PDA.
[d]Discontinue in the third trimester several half-lives prior to delivery.
[e]Only to be used in life- or organ-threatening disease, in the second or third trimester only.
[f]Life- or organ-threatening disease only.

[f]Life- or organ-threatening disease only.
[g]Conditionally recommend to discontinue in pregnancy.
[h]Low transfer in breastmilk.
[i]In doses >20 mg, breastfeeding should be delayed by 4 hours following consumption.
[j]Preferably use ibuprofen when needed.
[k]No data currently available but due to large size of molecule, minimal transfer in breastmilk anticipated.
[l]Limited data available, which suggests low transfer in breastmilk.
[m]No data available but small size of molecule suggests transfer into breastmilk likely.

NSAIDs: Non-steroidal anti-inflammatory drugs; PDA: patent ductus arteriosus.

Medication

One of the main causes of patient and physician concern during pregnancy is around medication usage. Certain medications used to treat RMDs are not safe in pregnancy;[22] however, this is not true for all medications as outlined by the American College of Rheumatology (ACR) guidelines (Table 3).[7] Despite this, many females with RMDs stop their RMD medication prior to conception or in the early stages of pregnancy.[23] Unfortunately, this increases their risk of flare, which requires rescue treatment with steroids followed by a period of unstable disease while their disease-modifying anti-RMD medication is restarted.[21] Open discussion with patients with RMD planning to conceive around pregnancy-safe medication, including the risks and benefits of stopping medication, could aid in limiting such situations.

This could also be an opportunity to ensure that the patient has commenced a prenatal vitamin. Females on folic acid antagonists including sulfasalazine will require higher doses of folic acid of 5 mg/day when trying to conceive through to the completion of the first trimester to decrease risk of neural tube defects.[24]

Many people with RMDs are treated with medications that are not compatible with pregnancy or have limited data for use in pregnancy.[22] For these patients, a period of transition to pregnancy-safe medications should take place prior to conception. It is important to remind those taking medications such as methotrexate and mycophenolate mofetil that these medications are not safe in pregnancy and to remind of the importance of using reliable contraception.

Autoantibody Status

Assessment for the presence of autoantibodies such as anti-Ro/SS-A, anti-La/SS-B, and anti-phospholipid status can determine pregnancy risk and need for additional medication during conception and pregnancy. Presence of anti-Ro or anti-La antibodies is associated with risk of fetal congenital heart block and development of neonatal lupus. Treatment of antibody-positive females during pregnancy with hydroxychloroquine significantly reduces this risk.[25]

Patients with SLE, history of recurrent miscarriage, or other severe pregnancy outcomes should be evaluated for presence of antiphospholipid antibodies (aPL).[20] This includes screening for β-2 glycoprotein 1, lupus anticoagulant, and anti-cardiolipin antibodies. Use of low-dose aspirin is recommended for patients with aPL to decrease risk of pre-eclampsia in pregnancy.[26] Once pregnant, patients with a previous history of obstetric or thrombotic antiphospholipid syndrome (APS) will require therapeutic or prophylactic low-molecular-weight or unfractionated heparin depending on their risk stratification.[7,27]

PREGNANCY

During the course of pregnancy, the female body undergoes a series of physiologic changes driven by dramatic alteration of hormone levels. These changes have varying effect on disease activity in RMD. Monitoring for signs of active disease is an essential component of care for the patient who is pregnant with RMD; however, accuracy of conventional tools to detect active disease can be limited by physiologic changes of pregnancy. An article outlining these challenges highlighted that a number of instruments have

been developed to more accurately assess disease activity in RMD pregnancies.[11]

While there are no specific guidelines for how often these patients should be seen by a rheumatologist during pregnancy, clinical assessment once per trimester allows regular monitoring of disease activity. More frequent monitoring may be required in cases of active disease, pregnancy complications, or underlying end-organ damage. Joint care of patients with RMD who are pregnant and regular communication between obstetrics and rheumatology can help to safely manage these challenging cases.

Systemic Lupus Erythematosus

Pregnancy in SLE is commonly encountered as this disease has a strong female predominance, with many diagnosed during their childbearing years. SLE can be difficult to monitor and manage due to the multi-organ involvement of autoimmune disease. This is further complicated by physiological changes of pregnancy, which can mimic disease activity, such as observed increases in erythrocyte sedimentation rate[28] or development of thrombocytopenia.[29] Other common pregnancy issues, including fatigue and proteinuria, can also be signs of active disease and confuse measures of disease monitoring. However, pregnancy has not been shown to affect presence of autoantibodies.

Disease activity is the most important predictor of pregnancy outcome in SLE, with 23.5% of patients experiencing active disease during pregnancy.[30] Pattern of organ involvement prior to conception accurately predicts organ involvement in pregnancy flares and can be helpful for targeted monitoring of disease activity.[31] There are a number of SLE scores that have been adapted for pregnancy including SLE Pregnancy Disease Activity Index (SLEPDAI),[32] Systemic Lupus Activity Measure (SLAM)-Revised, Lupus Activity Index in Pregnancy (LAI-P),[33] and the British Isles Lupus Assessment Group (BILAG) 2004 for pregnancy.[34]

Patients with lupus nephritis or renal impairment have an increased risk of further renal deterioration and adverse pregnancy outcomes.[35] This risk remains even in patients with previous lupus nephritis in remission at the time of conception.[4] Patients should be assessed for presence of hypertension, proteinuria, and raised serum creatinine >100 µmol/L routinely because of association with increased risk of adverse outcomes.[36] Risk for renal flare during pregnancy is associated with active renal disease at the time of conception, with a relative risk of 9.0 in cases of non-remission and a relative risk of 3.0 in partial remission.[37] To reduce risk of flare, disease activity should be controlled throughout pregnancy. This involves use of immunosuppressive medication, adequate blood pressure control, and use of low-dose aspirin to decrease risk of pre-eclampsia.[38] Renin–angiotensin blockers should be stopped prior to pregnancy or during the first trimester and changed to alternative hypertensive therapy.

Onset of SLE can occur during the course of pregnancy in patients with no previous history of connective tissue disease. Such cases have higher rates of thrombocytopenia, pregnancy loss, and active disease in pregnancy as compared to those with a previous diagnosis.[39] Higher rates of adverse maternal complications have also been seen in this population.[40] Prompt recognition and treatment is critical but can be a challenge due to the overlap of symptoms with that of normal pregnancy. Monitoring levels of complement and anti-double-stranded DNA antibodies can identify new-onset SLE in a patient who is pregnant. Certain clinical features, such as onset of renal impairment and hypertension prior to 20 weeks' gestation, are suggestive of SLE rather than pre-eclampsia.[17]

Autoantibody status is crucial for management of SLE pregnancies. In patients with SLE who have not had antibody status assessed prior to conception, this should be done as soon as possible in pregnancy along with an ECG. In cases of corrected QT prolongation or previous history of cardiac involvement, a baseline echocardiogram is useful to assess cardiac function. Females known to have anti-Ro or anti-La antibodies should be commenced on hydroxychloroquine to decrease risk of congenital heart block and neonatal lupus.[41] For those previously on hydroxychloroquine, continuation throughout pregnancy is strongly advised due to association with improved renal outcomes and decreased risk of both flares and thrombotic events.[42] Presence of anti-Ro antibodies will require serial fetal echocardiograms from Weeks 16–26 as per ACR guidelines.[7]

Pregnancy is a naturally prothrombotic event, requiring evaluation of need for additional anti-coagulation during this period. All patients with SLE should be screened for aPL and if positive commenced on low-dose aspirin in the first trimester. Previous history of obstetric APS requires commencement of prophylactic heparin, while history of previous thrombotic APS requires therapeutic heparin during pregnancy.[43] Positive aPL with no previous history can be managed with low-dose aspirin alone and close monitoring due to increased risk of pre-eclampsia.[7]

Active disease during pregnancy often requires a course of corticosteroids due to rapid onset of action. Frequency and duration of corticosteroid use should be limited due to potential increased risk of insulin resistance and infection. Evaluation of previous treatment and adherence must be considered prior to changing therapy. Hydroxychloroquine could be commenced but will take time to take effect. Azathioprine could also be considered. Current ACR guidelines recommend against the use of intravenous Ig (IVIG) due to limited evidence of benefit;[7] however, it has been previously deemed compatible with all stages of pregnancy including breastfeeding.[21] The European League Against Rheumatism (EULAR) guidelines also recommend consideration of IVIG in cases of severe refractory maternal disease in pregnancy.[44] Belimumab is the first biologic agent approved for use in the treatment of SLE, but unfortunately pregnancy data is not yet available to comment on its safety.

Rheumatoid Arthritis

Research in RA has demonstrated that the inflammatory arthritis commonly goes into remission during the course of pregnancy.[45] A recent meta-analysis reported improved disease activity in 60% of individuals during pregnancy, with 46.7% developing a flare in the postpartum period.[46] This is driven by a series of modifications of the maternal immune system, including downregulation of effector T-cell activity with an increase in regulatory T cells, to allow placentation and fetal growth.[47] Following delivery, these immunomodulatory effects dissipate with the decrease of pregnancy hormones, resulting in postpartum flares.

Although many pregnant patients with RA will experience improvement of disease activity during pregnancy, disease activity must be monitored as part of routine care. Physiological changes of pregnancy resulting in increased erythrocyte sedimentation rate,[28] fatigue, weight gain, and anaemia can all affect commonly used indexes such as the Disease Activity Score in 28 joints (DAS28) and Health Assessment Questionnaire (HAQ).[48] However, the DAS28-C-reactive protein 3, which excludes the global health score, has been shown to be the best clinical metric to detect active disease in patients with RA who are pregnant.[49] Ongoing research has shown that additional indices also perform well in this population, including the Rheumatoid Arthritis Disease Activity Index (RADAI) and the Clinical Disease Activity Index (CDAI).[50]

Risk of flare during pregnancy is commonly associated with medication cessation and active disease prior to conception.[23] There is no clear consensus on antibody presence and risk of flare in pregnancy. The Dutch Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study demonstrated a decreased risk of flare in people with RA who were pregnant and who did not carry autoantibodies.[51] However, a smaller study showed females with RA with active disease in pregnancy had higher levels of anti-citrullinated protein antibodies compared to those with lower disease activity.[52] Further studies are needed to characterise the relationship between RA antibodies and risk of flare in pregnancy.

Flare in RA during pregnancy requires prompt management as early recognition can result in improved pain control and rapid inflammation reduction. Often rescue therapy in the form of corticosteroids is required for a limited period. Review of current therapy and compliance can be helpful to determine alternative treatment options. In a patient who had previously come off treatment or had not been on treatment, discussion of treatment initiation with a pregnancy-safe medication (Table 1) is required.[7]

Spondyloarthropathy

Spondyloarthropathy (SpA) includes both axial SpA and psoriatic arthritis. Unfortunately, research on pregnancy in SpA is not as abundant as other RMDs. Research in axial SpA has revealed 47.8% of patients experience active disease in pregnancy,[53] with a peak in disease activity in the second trimester. Studies in psoriatic arthritis report quiescent disease during pregnancy with increased disease activity 6 months postpartum.[54] Similar to other RMDs, stable disease at conception was associated with favourable pregnancy outcomes.

Pregnancy can mimic many symptoms of SpA, including low back pain, night pain, and fatigue, but currently there are no validated indices for monitoring SpA activity during pregnancy. In a disease where clinical assessment of the spine is a core component of monitoring disease, this is a significant limitation. This is further complicated by mechanical strain of the increasing mass of the gravid uterus on the spine during the course of the pregnancy and postpartum period.[55] Further development of tools for monitoring SpA disease activity in pregnancy will provide much-needed insight into the effect of pregnancy on disease activity.

Ongoing development of national registers and collaboration between registers will allow for a rapid expansion of understanding of pregnancy in SpA. The European Network of Pregnancy Registers in Rheumatology (EuNeP) is a collaboration of four European national registers of patients with RMDs, formed with a focus on improving data collection on people with RMDs who are pregnant.[56] This collaboration has identified challenges in collection and comparison of pregnancy data, in addition to recommendations for streamlining of pregnancy data going forward.

Non-steroidal anti-inflammatory drugs are used to treat flares in SpA; however, these should be avoided beyond 32 weeks due to risk of premature closure of the ductus arteriosus.[57] Biologics such as TNF inhibitors are associated with stable disease in pregnancy and are recommended in pregnancy in the current ACR guidelines up to the third trimester, with the exception of certolizumab pegol, which can continue into the postpartum period.[7]

Systemic Sclerosis

Pregnancy in systemic sclerosis is uncommon as onset is typically after childbearing years. The primary concern in pregnancy is presence of PAH, which is the leading cause of maternal mortality.[58] Those considering pregnancy should be evaluated for PAH as part of monitoring and counselled when considering pregnancy. In cases of established PAH, patients should be strongly advised against pregnancy.[59] Patients with systemic sclerosis who achieve pregnancy have a higher prevalence of adverse pregnancy outcomes (odds ratio [OR]: 1.9 for miscarriage; 3.8 for low birth weight; 2.4 for preterm birth). However, optimisation of disease control prior to conception decreases this risk,[60] although progression of disease during pregnancy was observed in 14.3%. Close monitoring in specialist centres with support from obstetrics, rheumatology, and respiratory can aid in optimising outcomes.

Although now uncommon due to angiotensin-converting enzyme (ACE) inhibitors, there is a risk of scleroderma renal crisis in pregnancy. To avoid this, ACE inhibitors should be continued during pregnancy.[61] Prior to conception, a trial period on an alternative antihypertensive agent could be considered to optimise blood pressure control. In cases of hypertension, despite alternative medication, ACE inhibitors should be restarted. Low-molecular-weight heparin can reduce thrombotic risk, while sildenafil and epoprostenol are additional therapeutic options in pregnancy.[62] In cases of disease acceleration or rapid progression during pregnancy, additional life-saving therapies need to be considered, including preterm labour induction to allow use of additional medications not compatible with pregnancy.

Vasculitis

There are limited data on pregnancy in vasculitis because age of onset is typically beyond childbearing years, with a male predominance in most types of vasculitis. Disease activity in pregnancy varies by diagnosis, but all females with vasculitis should be considered for thromboprophylaxis during pregnancy. Pregnancy in these patients is associated with increased prevalence of pregnancy

complications, especially pregnancy loss and pre-eclampsia;[63] however, improved disease control prior to conception can improve outcomes.[64]

Patients with a new diagnosis or active disease prior to pregnancy are at higher risk of flares during pregnancy. Transitioning to pregnancy-safe treatment is essential to ensure stable disease during pregnancy. This is especially important as flares in eosinophilic granulomatosis with polyangiitis and microscopic polyangiitis can have high fatality rates.[65] A number of medications used to treat vasculitis are not compatible with pregnancy, leading to greater reliance on corticosteroids during this time. This should be limited when possible because of associations with adverse pregnancy outcomes, with increased reliance on low-risk medications including azathioprine and TNF inhibitors.[64]

Inflammatory Myopathies

The most common types of inflammatory myopathies are polymyositis and dermatomyositis. One study reported that 4–11% of females with these diseases had an onset age between 25 and 34 years.[66] Pregnancy complications in this population were associated with active disease during pregnancy (OR: 435.4) and onset of disease prior to pregnancy (OR: 9.36).[67] Relative risk of obstetric and fetal complications was 7.6 and 2.7, respectively, and were noted to occur more frequently following disease onset.[68] Hypertensive disorders in pregnancy have also been found to occur more commonly (OR: 2.90).[69] One analysis reported remission of disease during pregnancy, with active disease observed in 12.5%, but with notably 56.2% reporting postpartum flares.[70] Treatment in pregnancy is with IVIG and azathioprine, with limited use of glucocorticoids.[71]

POSTPARTUM

During the postpartum period, the mother's body again undergoes significant hormonal and physiological transitions as it recovers from the birth while adapting to breastfeeding.

This is compounded by the physical strain and sleep deprivation that comes with caring for a new infant. All of these factors can contribute to risk of postpartum flare. To minimise this risk, prompt re-evaluation of therapy is required.

A EULAR consensus statement in 2016 encouraged decisions on medication use during the postpartum period to maximise maternal benefit while minimising infant exposure.[44] The 2020 ACR guidelines includes a section on postpartum use and lactation,[7] highlighting the range of therapeutic options that can be safely offered to those breastfeeding to optimise disease control (Table 3).

CONCLUSION

Risk stratification and pregnancy planning are key to ensuring individuals with RMD have safe pregnancies with minimal risk of complications. This involves disease stabilisation, transition to pregnancy-compatible medications, assessment of autoantibody status, and evaluation of end-organ damage. Disease activity during the course of pregnancy varies by disease, with active disease in pregnancy associated with increased risk of pregnancy complications. The recent ACR guidelines detail the medications that are safe to use in pregnancy to control disease activity. Regular monitoring and communication between obstetrics and rheumatology is essential for maintaining stable disease in pregnancy and monitoring for complications.

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Clinical Manifestations and Diagnosis of Behçet's Syndrome

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Abstract

Behçet's syndrome (BS) is a systemic vasculitis with a wide range of clinical presentations and disease courses. It may involve the mucosa, skin, joints, vessels, eyes, and nervous and gastrointestinal systems. These organ involvements may present alone or co-exist in the same patient. Three main clusters of commonly co-existing manifestations were recognised and are currently called disease phenotypes. There is a significant heterogeneity among patients regarding demographic features and clinical expression of the disease that hinders a standardised disease assessment and a generalised use of diagnostic criteria. Additionally, BS is not associated with pathognomonic laboratory or histopathology features; therefore, the diagnosis is mainly based on the clinical manifestations. The purpose of this narrative review of the literature is to provide a description of the most common or typical clinical features of BS, summarise the major phenotypes of BS, and address the diagnosis strategy of this syndrome.

INTRODUCTION

Behçet's syndrome (BS) was first described by Hulusi Behçet in 1931, as a definite clinical entity, the 'triple symptom complex', based on three prominent signs: relapsing oral apthae, genital ulcerations, and iritis.[1] Although these are the most frequent manifestations, considered hallmarks of the disease, it was later recognised that BS is a multisystem inflammatory condition that may involve additionally the vascular, musculoskeletal, gastrointestinal (GI), and nervous systems.[2] The manifestations range from self-limiting symptoms, with unpredictable relapses, to severe clinical flares that may result in organ damage or death.

A variable vessel vasculitis is thought to underlie the clinical manifestations of the disease, although the presence of a vasculitis is difficult to discern in some of its features.[3] The exact aetiology and pathogenesis is poorly understood and BS is considered a multifactorial disease involving interactions of several genes such as the human leucocyte antigen (*HLA*)-*B51*, with unclear environmental exposures.

In line with such heterogeneity and uncertainties, the diagnosis of BS can be challenging. This narrative review focusses on clinical features

of BS, highlighting their specific value on the diagnosis of the disease.

METHODS

A PubMed search was conducted, using the keywords 'Behçet' AND 'manifestations', 'criteria', 'diagnosis', 'pathology', 'statistics', 'skin', 'eye', 'pulmonary', 'neurological', 'gastrointestinal', 'vascular', 'phenotypes', 'pathergy test', and 'HLA'. Original research articles (retrospective and prospective studies), systematic reviews, meta-analysis, and narrative reviews on the relevant topic published in the English language up to January 31st 2021 were included. A narrative review was performed giving priority to more recent, widely cited publications, as well as international guidelines, guided by the authors' experience.

EPIDEMIOLOGY

BS has its higher prevalence in the Mediterranean region, Middle East, and Far East Asia. Because of this peculiarity, it has been referred as the 'Silk Road disease'. In a meta-analysis by Maldini et al.,[4] a pooled prevalence was reported to be 10.3/100,000 globally, 119/100,000 for Turkey, 31.8/100,000 for the Middle East, 4.5/100,000 for Asia, 3.8/100,000 for North America, and 3.3/100,000 for Europe.[4] The prevalence of distinctive organ involvements also varies widely according to geographical regions and ethnic background (Table 1),[5-15] as well as according to sex and age.

Table 1: Clinical manifestations of patients with Behçet's syndrome from diverse world regions.

Country (N)	Oral ulcers	Genital ulcers	Skin	Pseudo folliculitis	Eye	Joint	CNS	Vascular	GI	Epididymitis
Spain[5] (n=496)	100	64	75	42	45	35	14	20	1	1
Greece[6] (n=82)	100	83	73	N/A	77	60	20	11	7	19
Italy[7] (n=396)	98	67	N/A	36	43	15	5	24	34	N/A
Germany[8] (n=747)	100	73	80	47	50	54	12	22	12	N/A
Egypt[9] (n=1,526)	100	85	49	N/A	71	49	13	24	10	N/A
Iran[10] (n=7,641)	98	64	62	51	56	38	10	9	7	5
Turkey[11] (n=2,313)	100	88	N/A	54	29	12	2	7	1	N/A
China[12] (n=1,996)	98	76	69	31	35	30	5	8	9	N/A
Korea[13] (n=1,527)	99	83	84	N/A	51	38	5	2	7	1
Japan[14] (n=3,044)	98	67	84	N/A	41	49	26	11	28	8
USA[15] (n=114)	100	99	79	41	49	74	7	17	5	N/A

CNS: central nervous system; GI: gastrointestinal; N/A: not applicable.
Data is presented as rounded percentages.

GI involvement, for example, is reported in 1–2% of cases in some Mediterranean regions, whereas frequencies around 30–40% are reported in Far East and in patients with northern European background.[10] BS most often develops in the third or fourth decade of life, but onset in childhood has been reported in 6–24% of patients.[16] Compared with adults, children have more frequent neurologic manifestations, particularly cerebral venous sinus thrombosis (CVST), GI involvement and family history of BS, and less frequent ocular manifestations.[17] The frequency of BS does not differ based on sex but there is difference in disease expression between sexes. Skin, eye, central nervous system (CNS), and vascular involvement are more common in males, whereas erythema nodosum (EN) and genital ulcers (GU) are more frequent in females.[18] The mortality rate is highest early after disease onset and significantly increased among younger men (<25 years of age).[19]

CLINICAL MANIFESTATIONS

Mucosa and Skin

Mucocutaneous lesions are the most common and usually the earliest manifestations. They include oral and genital ulcerations, papulopustular skin lesions, and nodular-like lesions.[20] Oral ulcers (OU) are generally the first and most common symptom,[2] occurring in almost all patients. They are usually small, painful, round, or oval erosions, mainly localised on the lips, buccal mucosa, tongue, and soft palate (Figure 1A). OU typically heal spontaneously in a few days to 2 weeks and without a scar.[21] Fatigue, stress, histamine-rich or -liberating food, local trauma, menstruation, and being a non-smoker have been reported as contributing factors for OU activity in BS.[22,23] They continue to develop for many years after disease onset, although the frequency of the episodes tends to diminish over time.[19]

GU are less frequent than OU but have a high discriminatory value on the diagnosis of BS.[2] They are usually located in the scrotum or in the major and minor labia (Figure 1B). More rare locations include the penis, vagina, cervix, inguinal, perineal, and perianal areas.[24] GU are painful at the initial phase, beginning as papules, pustules, or necrosis. They are usually deep and heal within 10–30 days, with formation of scars.[24] Unlike OU, GU tend to occur only in the early years following disease onset and disappear during the later course of the disease.[19]

Papulopustular lesions are also common features in BS. They are folliculitis- or acne-like lesions which appear as a papule, pustule, and comedons,[25] spontaneously healing in 2–3 days without scars.[20] These lesions are most commonly found on back, chest, lower limbs, and buttocks.[24]

EN-like lesions resemble classical EN, presenting typically with bilateral, pretibial, painful erythematous nodules. They can also be localised to the face, neck, forearms, and buttocks. They usually heal spontaneously in a few weeks, with residual hyperpigmentation.[24] Histological features of these lesions are a matter of controversy, but it was reported mixed or lobular panniculitis, infiltration of variable numbers of neutrophils, lymphocytes, and histiocytes and, unlike classical EN lesions, presence of vasculitis.[26,27]

Musculoskeletal

Characteristic symptoms are recurrent asymmetric mono- or oligoarthritis or arthralgia, usually involving large joints, especially knees, ankles, and wrists.[28] Joint involvement tends to be self-limited, typically leaving no deformity or erosion.[28] Sacroiliitis seems rare in patients with BS.[29]

Eyes

Ocular involvement is more frequent and severe in male patients.[30] It can be the first manifestation of the disease in 10–20% of the cases and typically presents during the first 2–3 years after the onset of extra-ocular signs.[31]

The most common eye manifestations are panuveitis (60.2%) and posterior uveitis (28.8%).[30] Anterior uveitis can occur but is rarely isolated and always non-granulomatous.[30] Initially, the involvement is unilateral with a remitting-relapsing course, then becomes bilateral.[32]

Retinal vasculitis and vitritis are the most common findings (Figure 1C).[30] Hypopyon, a visible sedimentation of neutrophils in the aqueous humour, is much less common although it was once considered a hallmark of BS.[30]

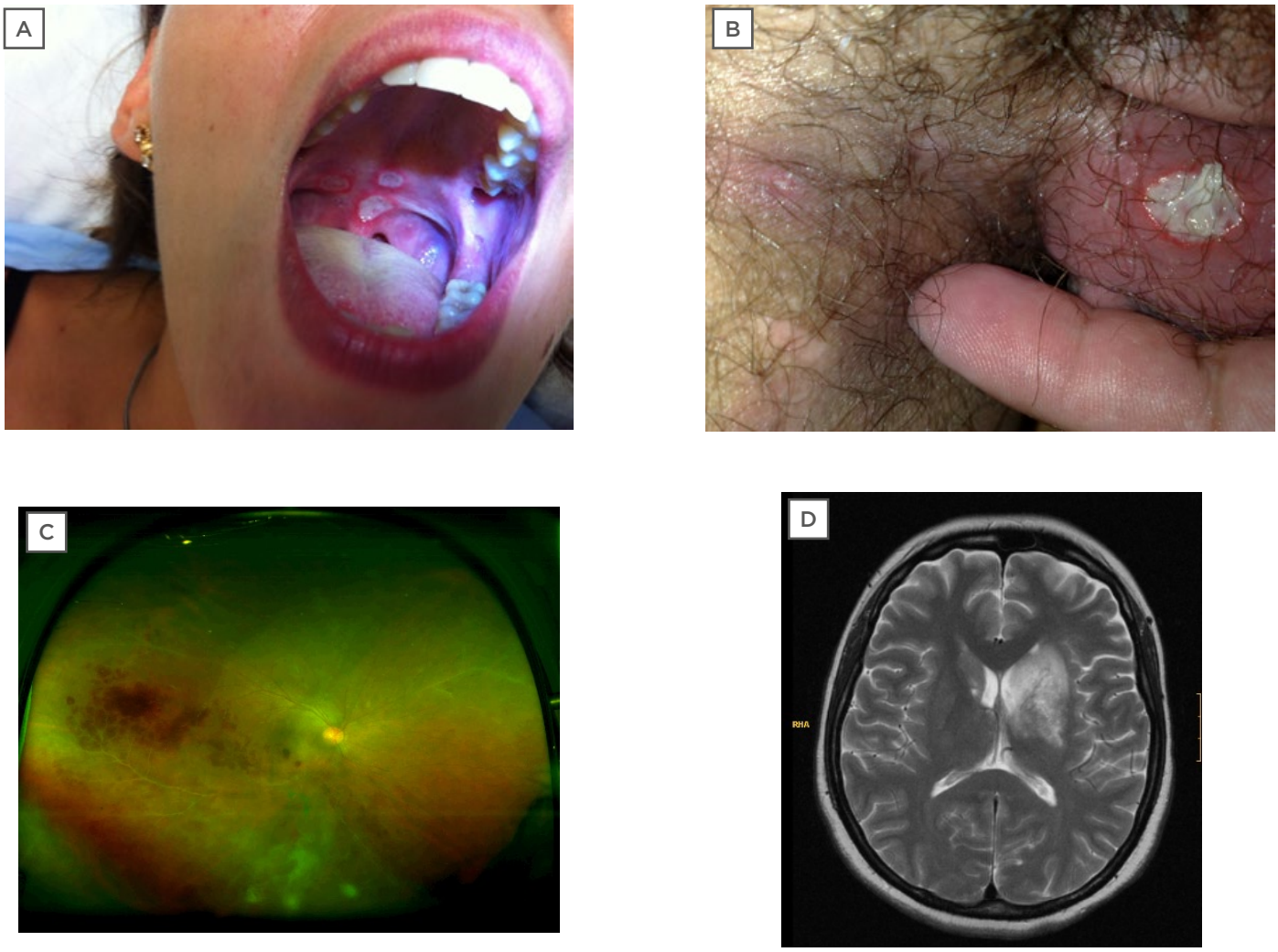

Figure 1: Examples of organ manifestations of Behçet syndrome.

A) Oral ulcers on the palate; B) genital ulcers on the scrotum; C) retinal vasculitis (ultra-widefield retinal imaging), with visible haemorrhages and contrast leakage; and D) large lesion, hyperintense on T2-weighted MRI, involving the basal ganglia and diencephalon, compatible with parenchymal neuro-Behçet syndrome.

Tugal-Tutkun et al.[30] recently proposed an algorithm for the diagnosis of Behçet's uveitis in adult patients, based on characteristic clinical findings. The items with higher accuracy for diagnosis of BS were superficial retinal infiltrate or its sequel, retinal nerve fibres layer thickness defect, signs of occlusive retinal vasculitis, diffuse retinal capillary leakage on fluorescein angiography, and absence of granulomatous anterior uveitis or choroiditis in patients with vitritis.[33] Additionally, with newer diagnostic technologies such as optical coherence tomography angiography, microvascular changes in the retinal vascular plexus, and choriocapillaris have been detected before the emergence of evident clinical findings even in patients with non-ocular BS.[34]

Ocular involvement is a significant cause of morbidity, although the prognosis has improved in the last 20 years. Tugal-Tuktun et al.[33] estimated the risk of loss of useful vision to be 6% at 1 year, 17% at 5 years, and 25% at 10 years.[30]

Nervous System

Neurological manifestations of BS are commonly referred as neuro-BS (NBS).[35] Its frequency among patients with BS is approximately 9%, being more common in male and younger patients.[36] It usually presents late in the disease

course, with a mean time between onset of BS and development of NBS ranging 3–6 years.[37] Rarely, it can precede other systemic features.[37]

The CNS is the usual site of neurological involvement.[35] There are two main categories of CNS involvement: parenchymal, which is more frequent and corresponds to an inflammatory meningo-encephalitic process; and non-parenchymal, which occurs secondary to vascular involvement.[35] These two subtypes occur very rarely in the same individual.[38]

Parenchymal-NBS usually presents with a subacute onset of brain stem, cerebral, optic, spinal cord, or diffuse syndromes, with manifestations such as pyramidal weakness, behavioural changes, headache, ophthalmoplegia, and sphincter changes.[35,39] It usually follows a relapsing–remitting pattern or a primary or secondary progressive course.[35] In parenchymal-NBS, cerebrospinal fluid (CSF) protein is usually modestly raised and the CSF cell count is raised in 60–80% cases, reported as neutrophilia, lymphocytosis, or mixed cellularity.[35] CSF glucose is usually normal.[35] MRI technique is the gold standard neuro-imaging modality for the diagnosis of NBS. A typical NBS acute or subacute lesion is large, isointense, or hypointense on T1-weighted, commonly enhanced with contrast, and hyperintense on T2-weighted, fluid-attenuated inversion recovery, and diffusion-weighted images.[35,36] It is preferentially located in the brain stem, but involvement of basal ganglia, diencephalon (Figure 1D) and internal capsule is also common.[36] On the other hand, chronic lesions are isointense on T1W images, smaller, and predominantly subcortical. Brain stem atrophy, particularly when asymmetric, is typical for chronic NBS and, if it is evident in the initial MRI, a progressive course could be expected.[35,36] Although rare, spinal cord lesions tend to be longitudinally extensive.[38]

Parenchymal-NBS may be difficult to differentiate from its mimics, particularly multiple sclerosis (MS). Some differential features can be listed: sensory symptoms, optic neuritis, internuclear ophthalmoplegia, and spinal cord involvement are more common in MS. In cases of MS, chronic white matter lesions tend to be supratentorial and periventricular with corpus callosum involvement, whereas in BS, lesions are bihemispheric, subcortical, and brain stem atrophy is characteristic.[2,38] In addition, CSF shows more cells in parenchymal NBS, while they are usually scarce in MS. Conversely to MS, intrathecal oligoclonal IgG bands have infrequently been reported in NBS (6.6–17.5% of patients); they are less stable in the setting of NBS compared to MS and can be easily suppressed by corticosteroid treatment.[35,36]

Non-parenchymal-NBS presents generally with CVST. A pseudotumour-like intracranial hypertension, acute meningeal syndrome, or acute stroke related to arterial thrombosis, dissection, or aneurysm, can also occur.[35] Patients with NBS-CVST usually present with headache for a few weeks, papilledema and, occasionally, sixth nerve palsy.[40] Cranial MRI scans usually show an occluded dural sinus but venous infarcts are rare.[40]

The prognosis of parenchymal-NBS is poor. In chronic parenchymal-NBS, a multicentre study revealed a fatal rate and bedridden state rate of 35.2% and 65.4%, respectively, at 200 months after the initiation of treatment.[41] A progressive course, a higher number of attacks, relapse after steroid tapering, and elevated protein and/or pleocytosis in the CSF were associated with a poorer prognosis.[42,43] CVST has, in general, a better prognosis.[36]

Vascular System

BS can affect both arterial and, most commonly, the venous vascular tree. Except the non-pulmonary arterial disease, vascular involvement usually presents within 5 years of disease onset.[44,45] The most frequent types of vascular involvement are superficial and deep vein thrombosis, affecting most commonly the lower extremities but also the superior extremities.[46] Thrombosis of atypical sites, such as inferior and superior vena cava, suprahepatic veins with Budd–Chiari syndrome, portal vein, cerebral sinuses, and right ventricle, are less frequent but quite unique to BS.[20] Post-thrombotic syndrome is common. A peculiar feature of BS is the very low possibility of embolism, probably because the chronic relapsing thrombotic events transform veins into dense fibrotic structures, forming a thrombus strongly adherent to the vessel.[10,44,45]

Arterial involvement in BS can be occlusive or, more frequently, aneurysmal. Aneurysms can occur in peripheral and visceral arteries.

Common locations are aorta, femoral, and pulmonary arteries. Presence of multiple lesions is frequent.[47] The co-occurrence of venous and arterial manifestations is common in BS. The contemporary occurrence of arterial pulmonary aneurysms and peripheral venous thrombosis is the hallmark of the Hughes–Stovin syndrome, now considered a form of vascular BS.[48] Screening of pulmonary artery aneurysms is important whenever anticoagulation is considered, in order to anticipate a massive haemoptysis.[49]

There is evidence that thrombus and aneurysm/pseudoaneurysm formation result from underlying vasculitis.[45] This is the reason why the European League Against Rheumatism (EULAR) recommends immunosuppressive treatment for the management of acute thrombosis, while the use of anticoagulation is controversial.[49] Although immunosuppressive treatment is effective in these manifestations, in the case of venous thrombosis, it has been described a relapse rate as high as 45% at 2 years despite treatment.[50] In the case of arterial lesions, a long-term outcome study reported a complete remission in only 38.6% of patients and a relapse rate of 27.7%.[47] Additionally, the vascular involvement in BS, particularly the pulmonary artery aneurysms had been identified as a leading cause of death in these patients.[19]

Gastrointestinal System

GI manifestations usually start 5–10 years after the onset of OU. The ileocecal area is the most commonly involved location (in up to 96% of cases), although the whole GI tract could be affected.[51] It typically presents with single or few, oval or round, large, and deep ulcers, with distinct borders, usually in a focal or multifocal distribution.[51] The most common symptoms include abdominal pain (87–92% of patients), followed by diarrhoea, and GI bleeding.[51] Acute abdomen findings such as perforation or GI bleeding were reported in a percentage as high as 30% of patients with GI involvement from BS.[52] Histologically, Behçet's ulcers contain non-specific chronic inflammation, and, eventually, a phlebitis.[52,53]

GI involvement in BS may be difficult to differentiate from Crohn's Disease. A comparative study revealed that round shape of the ulcers, five or fewer in number, focal distribution, and absence of aphthous or cobblestone lesions were significantly dominant features in BS.[54] Long-segment, intestinal obstruction, fistulas, and perianal abscesses were found to be significantly more frequent in Crohn's Disease.[55] GI involvement tends to have a recurrent course. Even with treatment, relapses may occur in approximately 20% of patients.[52]

Cardiac Manifestations

Cardiac involvement is very rare, described in 0.6% of patients in a large cohort in Iran.[10] Virtually all cardiac structures can be affected. There have been reports of coronary artery disease (with documented aneurysms and stenotic lesions, thrombus, or external compression by an aneurysm of a sinus of Valsalva), pericarditis, myocarditis, endocarditis and endomyocardial fibrosis, aortic regurgitation (caused by annular dilation and sinus of Valsalva aneurysm secondary to aortitis), mitral valve prolapse, and intracardiac thrombus (particularly in the right ventricle, and prone to recurrence).[56,57]

Pulmonary Manifestations

Pulmonary artery involvement (PAI) has a prevalence rate of less than 5%.[58] It generally consists of pulmonary aneurysms, but isolated pulmonary artery thrombosis has also been reported. Haemoptysis is the most common symptom. Cough, fever, chest pain, and dyspnoea can also occur. Pulmonary parenchymal lesions commonly accompany active PAI. They may present as nodules, consolidations, cavities, and ground-glass lesions.[59] Parenchymal lesions can be confused with opportunistic infections. However, studies have supported that parenchymal lesions are part of the PAI spectrum as they decrease significantly after immunosuppressive treatment and histopathological examination of the nodular infiltrations shows bronchiolitis obliterans organising pneumonia, granuloma, or infarction.[59]

Miscellaneous

Unusual manifestations have been reported. Some examples include orchiepididymitis, which is reported variably in different populations and generally follows other clinical manifestations of BS;[60] audio-vestibular system involvement, with sensorineural hearing loss and tinnitus;[61] and laryngeal manifestations, with potentially destructive ulcerations and stenosis.[62]

DISEASE PHENOTYPES

The above-mentioned organ involvements rarely occur as discrete BS manifestations and are commonly clustered. A number of cluster analyses and association studies identified significant associations among specific disease manifestations, reported as BS phenotypes. Three major BS phenotypes have been described. The presence of a phenotype can alert for the diagnosis, may help define molecular mechanisms leading to the co-development of different manifestations and could in the future guide a strategy for a personalised therapeutic approach.

Mucocutaneous and Articular Phenotype

There were a consistent proportion of patients present with both mucocutaneous and articular involvements. It was identified an association between papulopustular lesions and arthritis, and a strong association between EN and GU.[63] It was suggested that enthesitis was also part of this cluster. Additionally, mucocutaneous lesions of the genital area were found to be negatively associated with the presence of ocular and neurological involvements.[20]

Peripheral Vascular and Extraparenchymal Neurological Phenotype

In a previous study, a significant association was found between peripheral vascular disease and extraparenchymal neurological involvement.[44] In addition to this, approximately 80% of the patients with PAI were found to have concomitant venous thrombosis.[64] These associations suggest that events on both the arterial and the venous side of the vascular tree were likely sustained by similar pathogenic mechanisms. Vascular involvement has also been negatively associated with the presence of eye manifestations.[20]

Parenchymal Neurological and Ocular Phenotype

Growing evidence suggests an association between the posterior uveitis and parenchymal neurological involvement. Male sex and *HLA-B51*-positivity are features associated with this phenotype.[65]

DIAGNOSIS

Classification Criteria

There is no specific or pathognomonic biomarker, histopathology feature, or laboratory test for the diagnosis of BS; therefore, BS diagnosis is primarily clinical. Development of classification and diagnostic criteria have been an important focus in this field in order to categorise patients for study purposes and, in some cases, with the intent to guide an accurate diagnosis.

Classification and diagnosis criteria are produced using the same methodology, but they have different purposes. Classification criteria are intended to define a homogeneous population with similar clinical features, and, for that reason, they should have high specificity for the underlying disease while paying the price of losing sensitivity. Conversely, the goal of diagnostic criteria is to accurately identify as many individuals with the condition as possible, and therefore they should have high sensitivity and specificity, as well as high predictive measures. In theory, a diagnosis applies classification criteria to an individual patient but the diagnostic performance of any criteria depends on their sensitivity and specificity, and also on pretest probability of the disease, which reflects the prevalence of the disease and potential mimickers. In the case of BS, because of the wide clinical heterogeneity as well as the geographical and ethnic variation of prevalence and disease expression, it is difficult to accomplish universal diagnostic criteria that capture the full range of disease presentations and perform equally well in diverse populations.

Reflecting this challenging task, to the date of this article, 17 sets of diagnosis/classification criteria for BS have been proposed; the majority originating from different countries.[66] In general, they have OU, GU, and eye involvement in common. The first international criteria were the International Study Group (ISG) criteria for Behçet disease,[67] developed in 1990 with the collaboration of seven countries and being the most widely used thereafter. As a result of the low sensitivity of the ISG criteria observed in some validation studies, the International Team for the Revision of the International Criteria for Behçet disease (ITR-ICBD)[68] proposed new

criteria in 2014, with contributions from 27 countries. The ICBD intended to perform well regardless of the country and provide a useful tool to the identification of possible BS by non-experts. Compared to the ISG criteria, the ITR-ICBD consider different points for distinct manifestations, oral aphthae are not a mandatory criterion, and include vascular and neurological findings (Table 2). ICBD was shown to have much better sensitivity, 3% lower specificity, and better accuracy than ISG criteria.[66] The ICBD were then validated in Iranian patients[69] but its performance on a British cohort revealed a specificity of only 19%,[70] again advising caution on its use for diagnosis purposes in diverse clinical sceneries. Therefore, criteria have to be tailored to the practice setting and applied with clinical judgment. The pursuit of universal diagnostic criteria is now debatable, and subspecialty specific criteria have been proposed as a way to reduce the number of differential diagnosis in each particular scenery.[71]

Based on a childhood registry, a classification criteria for paediatric disease has been developed, called Paediatric Behçet's Disease criteria (Table 2).[72] In these criteria, all manifestations have the same weight, oral aphthosis is not mandatory, and a pathergy test is not considered.

Pathergy Test

The pathergy test is a non-specific hypersensitivity skin reaction induced by trauma such as a needle prick. Although there is no standardised procedure, it generally consists of an intradermal puncture on the skin with a 20-gauge or smaller needle into the patient's flexor aspect of the forearm.

Table 2: Comparison of the International Study Group, International Criteria for Behçet disease, and Paediatric Behçet's Disease criteria.

Criteria	ISG[67]	ICBD[68]	PEDBD[69]
Manifestations	Recurrent oral ulceration* Recurrent genital ulcers Ocular lesions† Skin lesions‡ Positive pathergy test	Oral aphtosis: 2 points Genital aphtosis: 2 points Ocular lesions:† 2 points Skin lesions:‡ 1 point CNS manifestations: 1 point Vascular disease:** 1 point Positive pathergy test (optional):‡‡ 1 point	Recurrent oral aphthosis:* 1 point Genital aphthosis: 1 point Ocular lesions:† 1 point Skin lesions:‡ 1 point Neurological disease:§ 1 point Vascular disease:** 1 point
Indicative of BS	Recurrent oral ulceration plus two out of the other four items	>4 points	≥3 points

*Oral ulceration needs to be recurrent and ≥3 in 12-month period for ISG and PEDBD.

†Defined as anterior and/or posterior uveitis and/or retinal vasculitis.

‡In ISG as erythema nodosum-like, pseudofolliculitis, papulopustular lesions, or acneiform nodules; in ICBD defined as erythema nodosum, pseudofolliculitis (pustulosis), or aphthous ulcers; in PEDBD as erythema nodosum, necrotic folliculitis, acneiform lesions.

§Excludes isolated headaches.

**In ICBD defined as arterial thrombosis, large vein thrombosis, phlebitis, and superficial phlebitis; in PEDBD as venous thrombosis, arterial thrombosis, arterial aneurysm.

††If pathergy testing is conducted, one extra point may be assigned for a positive result.

BS: Beçhet's syndrome; CNS: central nervous system; ICBD: International Criteria for Behçet disease; ISG: International Study Group; PEDBD: Paediatric Behçet's Disease.

It is considered positive when an indurated papule or pustule forms within 48 hours. Pathergy positivity is highly suggestive but not pathognomonic of BS, occurring for example in pyoderma gangrenosum, Sweet syndrome, and inflammatory bowel diseases.[73]

There are significant variations in the prevalence of pathergy among different populations. The positivity rate in BS is highest in countries along the Silk Road, and it is uncommon in Northern European and North American patients with BS.[74] Additionally, numerous studies have also demonstrated a decline in the prevalence of positive pathergy tests over the past decades.[10] Taking this into account, pathergy testing may be considered especially for patients who do not fulfil the criteria, standing near to the cut-off point, at least in countries with high prevalence of BS.

HLA-B51

BS is associated with the major histocompatibility complex *HLA-B51* allele. *HLA-B51* is carried by 34% to 64% of patients and increases the risk of BS development by a factor of 5.9.[75] Nevertheless, its prevalence varies across the globe, being higher in Asian, Middle Eastern, and Southern European populations, and lower in Northern Europe and North America.[75] Additionally, the presence of *HLA-B51* genotype among control healthy individuals ranges from 11% to 22%.[75] Although *HLAB51* allele is the most established risk factor for BS, it is neither necessary nor sufficient for its development. For these reasons, the diagnostic value of *HLA-B51* positivity is limited and it may be used as a supportive finding only in the presence of appropriate clinical findings.

The presence of *HLA-B51* seems to have some relation to disease expression. According to a meta-analysis, *HLA-B51/B5* is associated with significant increased prevalence of GU and ocular or skin involvement and with lower risk of GI involvement in BS.[76] Conversely, a recent large Japanese survey found that the presence of *HLA-B51* correlated negatively with the presence of GU.[14] In any case, clinical presentations of *HLA-B51*-positive and negative BS patients are not distinguishable.

CONCLUSION

BS is a complex and heterogeneous entity that does not fit perfectly into any recognised nosological group. OU are the most frequent manifestation, but the vascular and neurological involvements have the worst prognosis. Diagnosis is not straightforward because it is mainly based on clinical features. There are several classification criteria, often used to assist the diagnosis, but limitations should be considered. A solid knowledge of the typical manifestations and the local presentation of the disease is therefore essential to an accurate diagnosis. Current research focusses on the pathogenic mechanisms of the disease and its phenotypes, as well as on advances in laboratory and imaging techniques for diagnosis and monitorisation of BS. Shedding light on these topics may contribute to tailored therapeutic strategies and better outcomes in the future.

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Axial Spondyloarthritis: Clinical Characteristics, Epidemiology, and General Approaches to Management

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Abstract

Axial spondyloarthritis (axSpA) is a chronic inflammatory condition, with an age of onset almost exclusively under 45 years. Although symptoms are initially centred on the sacroiliac joints and spine, extraspinal manifestations are common and add considerably to the burden of disease. In this narrative review, the authors provide an update on the epidemiology of the disease and briefly summarise the pathophysiology. The authors detail the clinical manifestations of axSpA, including an overview of axial features, peripheral manifestations, and associated comorbidities. The authors outline the current outcome measures used in the assessment of patients. Finally, the authors provide a summary of the general principles of treatment and briefly outline the role of patient education in the management of individuals with axSpA.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory condition that predominantly affects the sacroiliac joints and spine. It is a type of spondyloarthritis (SpA) that refers to a group of inter-related conditions including psoriatic arthritis (PsA), reactive arthritis, and arthritis associated with inflammatory bowel disease (IBD).[1] Ankylosing spondylitis (AS) was the prototype SpA condition, diagnosed when characteristic changes of sacroiliitis are seen on an X-ray of the pelvis in conjunction with clinical criteria.[2] It has been increasingly recognised that the characteristic radiographic changes of AS could take many years to develop, thus excluding a large group of people with suggestive symptoms, but normal X-rays. This led to the development of the Assessment of SpondyloArthritis international Society (ASAS) criteria in 2009, which recognised a radiographic stage broadly similar to AS, as well as a non-radiographic stage (nr-axSpA).[3] This allowed individuals with earlier or less severe disease, who had suggestive clinical features and sacroiliitis on magnetic resonance imaging, to be classified as axSpA.

EPIDEMIOLOGY

AxSpA typically occurs in the third decade of life, and almost exclusively before 45 years of age. Historically, AS was considered to be a male-dominated disease, with early literature reporting

ratios of up to 10:1. However, more recent estimates put that ratio at closer to 3:1, with virtually no difference seen in the distribution of nr-axSpA between men and women.[4]

The major histocompatibility complex 1 human leukocyte antigen (HLA)-B27 allele is strongly associated with axSpA, and is found in 74–89% of affected individuals.[5] The prevalence of axSpA is typically greater in populations with a higher background prevalence of HLA-B27.4 In Europe, the prevalence of HLA-B27 varies from 2% to 25% and is highest in Scandinavian countries.[6] In contrast, HLA-B27 is rare in Japan and Arab countries, and almost non-existent in some populations such as indigenous tribes of South America.[6] The Pawaia tribe in Papua New Guinea has the highest prevalence of HLA-B27 worldwide, with 53% of people affected.[7]

In 2016, Stolwijk et al.[8] systematically estimated the global prevalence of axSpA between 0.36% and 0.70% and AS between 0.20% and 0.25%. The lowest prevalence was in Southeast Asia with a pooled prevalence of 0.2% and the highest in the northern Arctic communities. The native Eskimo (Inuit) population demonstrated a strikingly high prevalence of SpA of 2.5%, with the prevalence of HLA-B27 also high, affecting up to 40% of the study population.[9]

However, in reality it is difficult to know the true prevalence of axSpA because of a lack of population studies and a continued under-recognition and underdiagnosis of axSpA. In addition, delay to diagnosis has been a longstanding challenge in the management of axSpA, with mean delays of approximately 7 years reported in a large meta-analysis of 23,883 individuals.[10] Long delays to diagnosis are associated with a number of worse outcomes in axSpA, such as more active disease, greater chance of disability, and increased healthcare costs.[11] The delay to diagnosis is more common in women than men.[10] Women are less likely to report typical inflammatory back-pain symptoms, and more likely to report widespread pain; misdiagnoses such as fibromyalgia (FM) are more commonly made in the female population,[12] which may also exacerbate diagnostic delay. A negative HLA-B27 also appears to be associated with diagnostic delay.[13] If undiagnosed or under-treated, axSpA may lead to continuous pain, stiffness, and fatigue, and may ultimately lead to a reduction in quality of life (QoL).

PATHOPHYSIOLOGY

Most pathogenesis studies to date have focused on AS rather than axSpA. It appears to develop through complex interactions between genetic background and environmental factors. Studies performed on monozygotic twins and familial aggregation studies suggest that AS has a heritability of above 90%.[14,15] HLA-B27 positivity is also strongly linked with AS, occurring in only about 5% of the general population, but more than 90% of individuals with AS.[16] Exactly how HLA-B27 predisposes to AS is not yet fully understood, but several hypotheses have been put forward:[17]

1. Arthritogenic peptide hypothesis: the specific sequence of amino acids found in the peptide-binding groove of HLA-B27 might bind a peptide which elicits a cytotoxic T-cell response cross-reactive with a B27/self-peptide combination, i.e., molecular mimicry.[16]
2. HLA-B27 misfolding hypothesis: it is thought that the specific sequence of amino acids in the peptide-binding groove causes a propensity for HLA-B27 to misfold in the endoplasmic reticulum, leading to a pro-inflammatory stress response; however, evidence to date is largely limited to rat studies.[18]
3. Cell-surface B27 free heavy chain expression and immune recognition hypothesis: HLA-B27 tends to form homodimers, which bind to free heavy chains expressed on the cell surface, thus triggering a pro-inflammatory process.[16]

However, despite this strong association, HLA-B27 contributes only 33% of the total heritability of AS.[16] Genome-wide association studies have additionally detected several genes associated with AS.[19] Barrier damage to the skin or gut surfaces may also be relevant to pathogenesis.[20] Microbial infection appears to act as a triggering factor.[21]

Table 1: Three separate criteria for inflammatory back pain.

Calin criteria[25]	Berlin criteria[22]	ASAS expert criteria[26]
Age at onset <40 years Duration of back pain >3 months Insidious onset Associated with morning stiffness Improvement with exercise	Morning stiffness >30 min Improvement with exercise but not with rest Alternating buttock pain Waking in second half of night because of back pain	Age at onset <40 years Pain at night, with improvement upon getting up Insidious onset Improvement with exercise No improvement with rest
Criteria fulfilled if at least four of the five criteria are present, with specificity of 85% and sensitivity of 95%	*Criteria fulfilled if two or more parameters are fulfilled, with a sensitivity of 81% and specificity of 70%*	*Criteria fulfilled if four out of five parameters are present, with a sensitivity of 77% and specificity of 92%*

ASAS: Assessment of SpondyloArthritis international Society.
Italics refer to respective criteria fulfilment.

CLINICAL FEATURES

Axial Symptoms

Patients typically present with inflammatory back pain (IBP), characterised by an insidious onset of lower back and alternating buttock pain that worsens with inactivity and improves with exercise and non-steroidal anti-inflammatory drugs (NSAID). Patients may report waking at night with lower back pain, particularly in the latter stages of sleep. IBP is also associated with morning stiffness that usually lasts more than 30 minutes.[22] Determining whether lower back pain is inflammatory or mechanical can be challenging because lower back pain is very common in the general population, with 38% experiencing lower back pain for at least 1 day every year.[23] However, of all those with chronic lower back pain, IBP represents only approximately 5%.[24] Many attempts have been made to classify IBP (Table 1),[22,25,26] with the following features considered important in differentiating between IBP and other common causes of back pain:[22]

- Age: onset of axSpA after the age of 45 years is exceedingly rare.
- Duration of pain: non-IBP is often self-limiting.
- Onset of pain: non-IBP is often acute in onset.
- Diurnal variation: pain and stiffness in axSpA-related IBP tends to be worse in the second half of the night and early morning.
- Response to exercise: IBP responds well to exercise, a feature characteristic of many inflammatory conditions.
- Location: alternating buttock pain can indicate inflammation of sacroiliac joints.[22,26]

Peripheral Disease

Peripheral arthritis can affect up to half of individuals with axSpA, has a higher prevalence in the Latin American population compared to other geographic regions, tends to be more common in the lower limbs, and is typically oligoarticular.[27] Peripheral arthritis in axSpA may affect any joint, but is typically asymmetric. It is important to recognise peripheral arthritis, as its presence may direct management. Conventional synthetic disease-modifying antirheumatic drugs have a role in managing peripheral arthritis, whereas they are ineffective for axial disease.

Entheses are the sites of attachment of tendons or ligaments to bone, and enthesitis (inflammation of entheses) occurs in 44% of individuals with axSpA, with a predominance for lower limbs.[27] The heel (Achilles tendon or plantar fascia) is the most common site of enthesitis in axSpA, with most affected individuals having an intermittent course.[27] It can be difficult clinically to differentiate between enthesitis and arthritis, due to the anatomic overlap between entheses and joints.[28]

Dactylitis or 'sausage digit' involves inflammation of an entire digit (either a finger or toe), and is caused by flexor tenosynovitis, in combination with soft-tissue oedema.[29] Dactylitis can occur in up to 8% of individuals with axSpA,[27] although it is more commonly seen in PsA.[30] Interestingly, a meta-analysis explored the difference in the prevalence of peripheral manifestations between patients with AS and nr-axSpA and found no significant differences between the two groups.[31]

Extra-Articular Manifestations

Acute anterior uveitis (AAU), IBD, and psoriasis (PsO) are three conditions that are over-represented in axSpA and are thus considered extra-articular manifestations of the disease.

AAU is the most common extra-articular feature of axSpA, with a reported prevalence of 26–33%.[32] AAU associated with axSpA typically presents acutely, often with a 1- to 2-day prodrome, and tends to be unilateral, with circumlimbal hyperaemia, pain, photophobia, and visual impairment, with subsequent attacks often affecting the other eye. AAU more commonly occurs in a *HLA*-B27-positive patient cohort.[33] Visual prognosis in AAU associated with axSpA is excellent, with most individuals regaining full vision within 2 months.[34]

PsO is another notable feature of axSpA, affecting approximately 10% of individuals.[32] This disease feature must be distinguished from a diagnosis of PsA, which may present similarly. Patients with axSpA tend to have more back pain at presentation and score higher on physician score global indices when compared to PsA.[35] Interestingly, the presence of PsO in axSpA is an independent risk factor for increased entheseal damage.[36]

Clinically evident IBD is noted in 6–14% of AS patients,[32] with Crohn's disease occurring more commonly than ulcerative colitis. However, microscopic evidence of IBD was noted in up to 60% of AS patients, suggesting a significant proportion of clinically silent disease.[37] Faecal calprotectin is a non-specific marker for gut inflammation. In a 5-year longitudinal study, higher faecal calprotectin levels at baseline were associated with the development of Crohn's disease, as well as more severe AS disease clinically, but without any relationship to gut symptoms, suggesting that inflammation in the gastrointestinal tract and musculoskeletal system are linked.[38]

COMORBIDITY IN AXIAL SPONDYLOARTHRITIS

Mortality in axSpA is increased when compared with age- and sex-matched controls.[39,40] Some of this excess mortality can be explained as a direct consequence of the disease, such as death because of neurological deficits from vertebral fractures.[41] However, comorbid conditions, in particular cardiovascular disease, are shown to be a leading cause of death in axSpA.[39,40]

A comorbid condition can be defined as any distinct additional clinical entity that has existed or that may occur during the clinical course of an individual who has the index disease under study.

The ASAS-COMOSPA study was a large, multinational, cross-sectional study that outlined the profile of comorbidities occurring in individuals with SpA.[42] The most prevalent comorbidity was osteoporosis, affecting 13% of the cohort. Diagnosis of osteoporosis in axSpA using dual-energy X-ray absorptiometry may be difficult in advanced structural disease because of the presence of osteoproliferation, which can falsely increase bone mineral density. Lateral views of the spine are a promising technique for overcoming this.[43]

Almost 4% of the ASAS-COMOSPA cohort had cardiovascular morbidity,[42] with a lower prevalence in axSpA individuals compared with those with peripheral SpA.[44] Hypertension and smoking have been shown to be more pervasive in an axSpA population.[45]

Depression is common in axSpA, with Zhao et al. reporting a prevalence of 15% showing at least moderate depression in a systematic review.[46] Obesity is another comorbidity that is shown to be common in axSpA, affecting 15–27% of axSpA cohorts.[47,48] Of note, patients with concomitant obesity tend to be less responsive to conventional therapy in axSpA.[49]

Comorbidities in axSpA are of clinical relevance, as they have been shown to add to the burden of disease. Increasing comorbidity burden is associated with more active disease and worse spinal mobility.[47] The presence of comorbidities

in SpA adversely affects physical function, work ability, QoL, and increases healthcare expenditure.[47,50] Despite this known burden of comorbidities in axSpA, optimal screening for them is poor, with the ASAS-COMOSPA study demonstrating that only half of participants had an adequate assessment of their cardiovascular status, and optimal cancer screening was only performed in 11–44% of participants.[42] Less than 20% of individuals with axSpA have an objective assessment of their bone mineral density.[47] Treatment of comorbidities is also suboptimal, with less than one-quarter of a Dutch cohort of patients with AS treated for hypertension or hypercholesterolaemia achieving treatment targets.[45]

FM is a non-inflammatory comorbidity characterised by widespread pain and fatigue, with an estimated one-in-six prevalence in axSpA.[51] Patients who met the criteria for FM reported significantly worse disease activity and function, as well as a lower QoL.[52] In patient-reported outcomes (PRO), low disease activity or disease remission is less likely to be achieved in patients with FM.[53] The presence of FM appears to have a negative impact on response to biologics,[54] with shorter retention times.[55] For this reason, it is important to screen patients with AxSpA for FM because it may affect patient outcomes.

OUTCOME MEASURES

AxSpA is a complex multifaceted condition, and assessment of outcomes must reflect this. A number of validated outcome measures have been developed in axSpA, which deliver a comprehensive overview, subjectively and objectively, of many different domains of disease. Here, the authors collate scoring systems in axSpA that detail disease activity, patient function, QoL, radiological assessment, as well as objective measurement of enthesitis and dactylitis.

Bath Ankylosing Spondylitis Disease Activity Index

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a validated PRO that measures fatigue, spinal pain, peripheral joints, enthesopathy, and early-morning stiffness severity and duration on a scale of 0–10.[56] Scores of 4 or greater suggest active disease, which may require alteration of therapy.[57] The benefit of the BASDAI is that it is a simple, patient-focused assessment assessing a wide variety of axSpA features. One of its drawbacks is that objective evidence of inflammation such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) is not assessed in the BASDAI. While the BASDAI did not initially include nr-axSpA patients, it has since been suggested that it may also be used in this patient cohort.[58]

Bath Ankylosing Spondylitis Functional Index

The Bath Ankylosing Spondylitis Functional Index (BASFI) is a patient-reported assessment for everyday tasks, also scored on a scale of 0–10, using either a numerical or a visual analogue.[59] This scoring tool is validated, quick and easy to use, and sensitive to changes in the disease.[60] Similar to the BASDAI, this tool had initially been validated for AS and not nr-axSpA.

Ankylosing Spondylitis Disease Activity Score

The Ankylosing Spondylitis Disease Activity Score (ASDAS) was developed to include objective measures of inflammation that were not present in the BASDAI. It is closely associated with the Disease Activity score utilised in rheumatoid arthritis. The ASDAS incorporates three questions from the BASDAI (back pain, peripheral pain, and early-morning stiffness), patient global assessment, and acute-phase reactant using either ESR or CRP.[61,62] Disease activity is subsequently classified into inactive, moderate, high, and very high disease activity states.[63] The ASDAS has demonstrated validity and is more sensitive to treatment than previous scoring metrics.[64] A notable disadvantage of the ASDAS is CRP or ESR may not be available on clinic days. Also, a raised CRP or ESR may not always reflect disease activity.

Health Assessment Questionnaire

The Health Assessment Questionnaire (HAQ) is a PRO questionnaire, which initially focused on pain, disability, medication effects, costs, and mortality. Answers are assessed from 0–3, where 3 indicates more severe disability.[65]

Ankylosing Spondylitis Quality of Life

The Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire is comprised of 18 questions that aim to accurately assess QoL in patients with AS.[66] It may also be used in nr-axSpA. Each question is yes/no, with each 'yes' scoring one point. The points are summed, giving a total score between 0 and 18, with a higher score signifying a worse QoL. Difficulties with the AS QoL include failure of a yes/no answering system to fully encapsulate a patient's sense of wellbeing.

Bath Ankylosing Spondylitis Metrology Index

The Bath Ankylosing Spondylitis Metrology Index (BASMI) differs from previous scoring systems in that it assesses objective clinical measurements rather than PRO. BASMI assesses spinal mobility on a scale of 0–10.[67] The composite score measures cervical rotation, wall-to-tragus distance, lateral flexion, modified Schober's test, and intermalleolar distance. Higher scores reflect more significant restriction. It is a quick and reproducible assessment that demonstrates high sensitivity.

Modified Stoke Ankylosing Spondylitis Spinal Score

The Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) was developed to assess radiographic changes in AS.[68] It uses lateral spinal X-rays to quantify radiological damage on the anterior aspect of the spine from the lower border of C2 to the upper border of T1, plus the lower border of T12, all five lumbar vertebrae, and upper sacrum. This scale scores each vertebra border on a 0–3 scale: 0 is normal; 1 shows sclerosis erosions or squaring; 2 is for obvious syndesmophyte formation; and 3 shows total bridging syndesmophyte formation. A summed score of 0 indicates a normal spine, and 72 a completely ankylosed, or 'bamboo', spine.

Maastricht Ankylosing Spondylitis Enthesitis Score

The Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) is a scoring system of enthesopathy in patients with spondyloarthritis. Thirteen sites are assessed for discomfort on clinical examination in binary terms of tender or non-tender.[69] This scoring system is more user-friendly than previous enthesitis measurements such as the Mander Enthesis Index (MEI). High enthesitis scores correlate well with high disease activity scores.

Leeds Dactylitis Instrument

The Leeds Dactylitis Instrument (LDI) is a validated clinical measurement of dactylitis. Dactylitis was defined as an increase of 10% or more of the size of the contralateral unaffected digit.[70] Measurement of degree of tenderness is also assessed clinically in order to complete the score. High scores are associated with worse dactylitis.

GENERAL TREATMENT OVERVIEW

Although a detailed overview of treatment is beyond the scope of this narrative review, the authors here outline the general principles of management of axSpA, based on existing recommendations (Figure 1).[58,71] Briefly, the management of axSpA may be classified into non-pharmacological and pharmacological treatment, and treatment should be tailored according to the manifestations of the disease, the severity of symptoms, the clinical status of the patient, and the expectations and wishes of the patient.[58] The importance of regular exercise and avoiding smoking must be emphasised to each patient, regardless of other treatment modalities. If the patient is symptomatic, regular NSAIDs are typically the first line of pharmacological treatment. If there is insufficient response with NSAIDs, patients with predominantly axial disease should be assessed for biologic disease-modifying anti-rheumatic drugs. Currently, anti-TNFs, anti-IL-17, and JAK inhibitors are licensed for axSpA treatment (Table 2).

THE ROLE OF THE PATIENT IN DISEASE MANAGEMENT

For too long, patients were often excluded from decisions regarding management of their condition. This has been addressed with the publication of the European League Against Rheumatism (EULAR) recommendations for patient education in inflammatory arthritis.[72] Shared decision-making between the patient and rheumatologist is now an overarching principle in the recommended management of axSpA.[58]

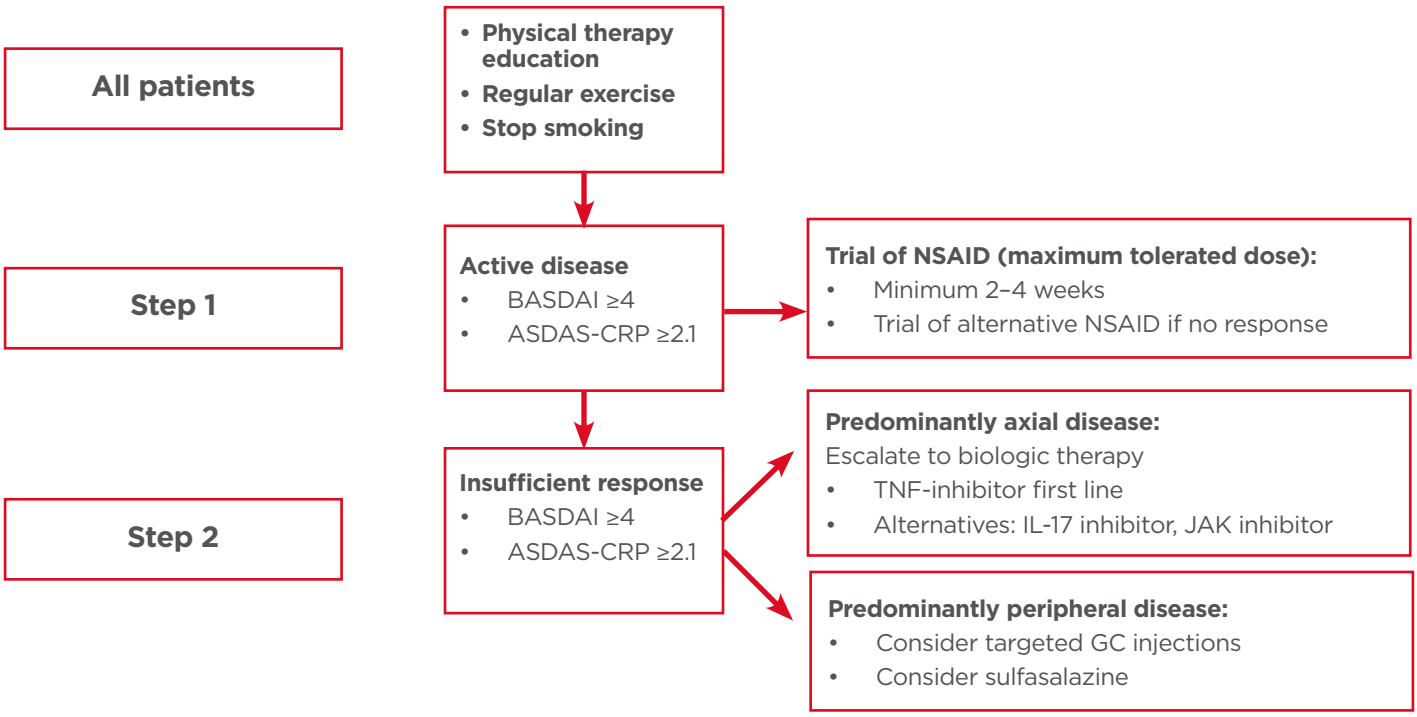

Figure 1: Steps for all patients taking part in physical therapy education, regular exercise, and who have stopped smoking.

ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score–C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; GC: glucocorticoid; NSAID: non-steroidal anti-inflammatory drug.

Table 2: Indications for biologics and JAK inhibitors.

	Axial SpA	Acute anterior uveitis	Psoriasis	Crohn's disease	Ulcerative colitis
Infliximab	Yes	Yes	Yes	Yes	Yes
Adalimumab	Yes	Yes	Yes	Yes	Yes
Etanercept	Yes	No	Yes	No	No
Certolizumab	Yes	Yes	Yes	Yes	Yes
Golimumab	Yes	Yes	Yes	No	Yes
Secukinumab	Yes	No	Yes	No	No
Upadacitinib	Yes	Insufficient data	Yes	Insufficient data	No
Tofacitinib	No	Insufficient data	Yes	No	Yes

SpA: spondyloarthritis.

To ensure that the patient can partake in all elements of this shared decision, education is key and refers to all activities that ensure an individual is well-informed about their condition, from education about treatment options to general health education and health promotion.[72] Patient education, which can range from patient information leaflets to structured educational programmes, has been shown to increase adherence to treatment and promote patient self-management.[73]

The rheumatology nurse plays a key role in educating patients, with the updated 2018

EULAR guidelines recognising the importance of rheumatology-trained nurses in providing needs-based education to individuals affected with chronic inflammatory arthritis.[74] The Educational Needs Assessment Tool (ENAT) is one instrument that can accurately assess an individual's educational need and has been validated in many rheumatic conditions, including AS.[75] Using the results of the ENAT to guide the education of a patient can lead to improved outcomes.[76] However, the ENAT alone is not sufficient, and the focus should be placed on individualised patient education, which should be tailored according to their needs.[74]

One area where patient education is particularly key is in promoting the role of physical exercise in axSpA. Although the most effective exercise protocol in axSpA has not been clearly established, physical exercise is shown to improve disease activity and physical function in individuals with SpA. Despite this, physical activity is lower in adults with axSpA compared to the general population, with higher disease activity levels in those who are less physically active.[77] Many individuals with axSpA lack motivation to partake in physical activity, even when aware of the benefits.[78] Additionally, many individuals with rheumatic conditions are unaware of physical activity guidelines.[79] A 3-month behavioural intervention in axSpA that incorporated motivational interviewing techniques resulted in better QoL, spinal mobility, and physical activity levels in patients with axSpA compared to a control group, which was sustained at Month 6.[80] This highlights the positive role that patient education can play in the management of axSpA.

CONCLUSION

In summary, axSpA is a chronic inflammatory condition, with both spinal and extraspinal manifestations. Recognition of IBP can be challenging, but the most recent ASAS IBP criteria have increased the sensitivity and specificity of the classification criteria. HLA-B27 is thought to play a significant role in the pathophysiology, but more research is needed to fully elucidate the pathways. Awareness of extraspinal manifestations of axSpAis is low, as shown by the infrequent screening that occurs. Regularly assessing multiple different disease outcomes with validated tools is an important part of managing axSpA, and assessing the effect of treatment. Enhancing patient involvement in their own management is also key.

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Treat to Target in Spondyloarthritis: Myth or Reality?

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Abstract

A treat-to-target (T2T) strategy is a treatment plan in which the clinician treats the patient aggressively enough to reach and maintain explicitly specified and sequentially measured goals. To apply a T2T strategy, some conditions should be met. First, a proactive, clear endpoint should be used and a threshold should be defined. Second, a choice between several effective therapies must be available. Third, the endpoint should be supported by findings from randomised controlled trials supporting early aggressive treatment. Fourth, the strategy should be cost-effective. Finally, it needs to be acceptable by the stakeholders.

The objective of this review was to verify if the conditions for applying the T2T strategy were met in psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), using a narrative review.

Based on the currently available literature, the conditions for applying the T2T in PsA and axSpA were partially met. First, proactive outcome measures are available; however, there is no clear consensus regarding the optimal one. Second, there is a reasonable choice of approved therapies for both diseases. Third, additional randomised controlled trials demonstrating the effectiveness of a T2T approach are still needed. Fourth, cost-effectiveness studies are needed and should include patients from different healthcare systems. Fifth, the implementation of T2T recommendations in routine care and the adherence to its application in clinical practice should be promoted.

In summary, preliminary data suggest that T2T might be beneficial to patients with PsA and axSpA. However, further studies are needed to meet all the criteria before strongly advocating for T2T strategies.

INTRODUCTION

A treat-to-target (T2T) strategy is a treatment plan in which the clinician treats the patient aggressively enough to reach and maintain explicitly specified and sequentially measured goals, such as remission, low disease activity, or absence of disability.[1,2]

The T2T concept was broadly used in non-rheumatological diseases, such as hypertension,[3] diabetes,[4] and dyslipidaemia[5] and has shown to improve important clinical outcomes such as preventing cardiovascular events, diabetic retinopathy, and even ultimate outcomes such as mortality.

In rheumatology, T2T was applied successfully in rheumatoid arthritis,[6] in gout,[7] and in systemic lupus erythematosus,[8] with clear target cut-offs in disease activity scores and serum urate levels, respectively, correlating with the prevention of radiographic damage.[9,10]

Specific recommendations for T2T in rheumatology were first developed in rheumatoid arthritis in 2010,[6] followed by recommendations for spondyloarthritis (SpA; including ankylosing spondylitis [AS] and psoriatic arthritis [PsA]) in 2012, which were later updated in 2017.[11] They were adopted, although conditionally, in the international management recommendations for PsA[12,13] and axial spondyloarthritis (axSpA).[14,15] In addition to the goal of optimising the quality of life by decreasing symptoms, inflammation, and structural damage, the T2T recommendations in SpA must face an additional challenge: they must address extra-musculoskeletal manifestations (EMMs) as possible targets, which makes the 'target' a much more heterogeneous and complicated one.

To apply a T2T strategy, some general conditions should be met (Table 1). First, a proactive, clear endpoint, which is the treatment aim, should be used in a specific target algorithm and a threshold should be defined. Second, a choice between several effective therapies that allow the clinical goal to be achieved must be available. Third, the endpoint should be supported by findings from randomised controlled trials (RCTs) suggesting that early aggressive treatment approaches are advantageous. Fourth, the proposed strategy should be cost-effective. Fifth, it needs to be acceptable by the stakeholders.[16]

Although the T2T approach is well established in RA, its relevance and applicability in PsA and axSpA are still debated.

OBJECTIVE

The objective of this review was to verify if the conditions for applying the T2T strategy were met in PsA and in axSpA.

METHODS

Using the key words "treat to target", "rheumatology", and "spondyloarthritis" in PubMed, the authors conducted this narrative review. First, the authors identified the conditions that are required to apply a T2T strategy and summarised them in five questions.

Table 1: Summary of conditions needed to apply a T2T strategy in psoriatic arthritis and axial spondyloarthritis.

Conditions for T2T	Psoriatic arthritis	Axial spondyloarthritis
Is there a proactive, clear endpoint, which is the aim of the treatment?	+ (A consensus regarding the best target is needed)	+ (A consensus regarding the best target is needed)
Is there a choice of several effective, available therapies that allow the clinical target to be reached?	+	+
Is the endpoint supported by findings from RCTs suggesting that early, aggressive treatment approaches would be advantageous?	+/- (One RCT, soft endpoints)	+/- (One RCT, soft endpoints)
Is the strategy cost-effective?	- (One RCT)	+ (One RCT)
Is the strategy acceptable by the stakeholders?	+/-	+/-

RCT: randomised controlled trial; T2T: treat-to-target.

Then, the responses to these five questions were sought for PsA and axSpA, respectively.

Is there a proactive, clear endpoint, which is the aim of the treatment?

A 'good' endpoint or target must be easily measurable in clinical practice, be validated in patients with PsA and axSpA, respectively, and reflect clinical outcomes that are important to both patients and physicians. The choice of the target should be a shared decision between the patient and the rheumatologist, considering all relevant situational factors. Treatment, once started, should be monitored to investigate if the endpoint is reached. The endpoint should be used in a specific target algorithm, and a threshold should be defined. Since both diseases, particularly PsA, are very heterogeneous, encompassing arthritis, enthesitis, dactylitis, and/or psoriasis in the same patient, finding the optimal target is challenging.

The targets can be soft, reversible outcomes (i.e., disease activity score or inflammatory markers) or hard, irreversible outcomes (i.e., radiographic damage or disability).[11] In most cases, soft endpoints correlate with the hard outcomes while being easier to obtain, thus often serving as surrogate measures for the hard, more relevant outcomes.[17-21]

Moreover, the clinician must keep in mind the EMMs and take them into account when facing a specific clinical situation.

Is there a choice of several effective, available therapies that allow the clinical target to be reached?

A treatment is usually considered effective when its value has been demonstrated by high-quality RCTs. For the current analysis, the authors included the therapies that are recommended by international rheumatology bodies such as the American College of Rheumatology (ACR)/National Psoriasis Foundation (NPF),[13] the European Alliance of Associations for Rheumatology (EULAR),[12,14] the Assessment of Spondyloarthritis International Association (ASAS),[14] and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).[22]

Any therapy whose efficacy was demonstrated in a recent RCT published after issuing these recommendations was also evaluated. Non-pharmacological treatments were evaluated, as well as a mean to treatment optimisation.

Is the endpoint supported by findings from RCTs suggesting that early aggressive treatment approaches would be advantageous?

RCTs comparing the T2T strategy to the standard of care in PsA and axSpA, respectively, were reviewed.

Is the strategy cost-effective?

Cost-effectiveness studies were analysed from the identified RCTs.

Is the strategy acceptable by the stakeholders?

Acceptability was first evaluated by checking if the T2T strategy was adopted in the PsA and the axSpA recommendations (ACR, ASAS, GRAPPA, and EULAR). Second, studies regarding the implementation of T2T in clinical practice and its related perceptions by patients and by healthcare providers (HCP) were analysed.

Finally, strategies for implementing and adopting T2T in clinical practice were discussed, and the unmet needs and areas for future research were identified.

RESULTS

Psoriatic Arthritis

Is there a proactive, clear endpoint, which is the aim of the treatment ?

Many composite measures exist and can be potential candidates for use as a proactive endpoint.[11,23] These measures include ACR outcome measure, Arithmetic mean Desirability Function (AMDF) composite score, Composite Psoriatic Disease Activity Index (CPDAI), Disease Activity in Psoriatic Arthritis (DAPSA), Disease Activity Score 28 joints (DAS-28:), Group for Research and Assessment of Psoriasis and Psoriatic Arthritis Composite Index (GRACE), Minimal Disease Activity (MDA), Psoriatic Arthritis Disease Activity Score

(PASDAS), Psoriatic Arthritis Response Criteria (PsARC), Routine Assessment of Patient Index Data 3 (RAPID3), and Very Low Disease Activity (VLDA) (Table 2). All of these measures include joint counts: tender (TJC) and swollen (SJC). Many scores include the patient's and/or the physician's global assessment; some of them include inflammatory markers, skin outcomes, or evaluation of dactylitis, enthesitis, or axial involvement.

Overall, according to two systematic literature reviews, there is an important heterogeneity regarding the composite outcome measure used in PsA studies; therefore, a consensus in this area is a clear unmet need.[24,25] In a GRAPPA meeting including 26 rheumatologists, dermatologists, and patient research partners, the panel could not reach a consensus regarding a continuous measure of disease activity.[23]

A comparison of remission and low disease activity states with DAPSA, MDA, and VLDA in a clinical trial setting in patients with PsA concluded that both DAPSA and MDA composite measures (Table 3) can be used for evaluation of the status and treatment response utilising a T2T approach and can improve patient health-related outcomes. These two measures were also the ones that were preferred in the 2017 T2T recommendations.[11] Likewise, in a clinical trial setting of the study using DAPSA and MDA in secukinumab-treated patients with PsA, both composite measures were useful for evaluation of the status and treatment response utilising a T2T approach.[26]

On the one hand, the DAPSA was initially developed for reactive arthritis.[27] It has been validated for use in PsA, where it showed correlational, discriminatory, and criterion validity; furthermore, it was sensitive to change in trials and observational studies alike and has shown a good correlation with ultrasound-assessed synovitis.[28,29] Schoels et al.[30] provided criteria for disease activity states and treatment response, which showed good performance in clinical trials and observational data. It is a simple measure and specifically measures peripheral arthritis without the inclusion of any other domains. Therefore, a separate assessment of skin disease and potentially other domains should be mandated alongside the DAPSA score to ensure a full assessment of PsA disease activity. DAPSA use was recommended by the T2T 2017[11] and the ACR 2018[13] PsA management recommendations.

On the other hand, the MDA encompasses several disease domains (joint counts, global assessment, skin assessment, HAQ, enthesitis) and is increasingly accepted. The MDA criteria were specifically developed with the idea of investigating the benefits of T2T in PsA[31] and were validated in PsA in 2010 and used as a key outcome measure in the main T2T trial in PsA.[32] MDA use was recommended by the GRAPPA 2015,[22] the T2T 2017,[11] and the ACR 2018[12] management recommendations. In a recent analysis, Mease et al.[33] compared the disease control thresholds in the Corrona PsA/axSpA registry. They confirmed the previously described notion that MDA and VLDA were the most stringent disease activity measures and resulted in overall lower disease activity in multiple key domains compared to patients who met clinical DAPSA, Patient Acceptable Symptom State (PASS), Patient Global Assessment of Arthritis (PtGA), and Patient Global Assessment of Arthritis and Psoriasis (PtGA PA) thresholds.[25] Therefore, they encouraged the rheumatologists to use MDA/VLDA to assess disease control in patients with PsA.

Furthermore, since PsA is a very heterogeneous disease, recent head-to-head trials have used combined outcomes to reflect the complexity of the disease, including targets in the joint (ACR) and the skin measurements (Psoriasis Area and Severity Index; PASI) that must be reached simultaneously.[34,35] This approach has helped distinguish some patients' profiles where a specific therapeutic class can be effective. Moreover, patients simultaneously achieving ACR 50% improvement (ACR50) and PASI 100% improvement (PASI100) had consistently better improvements in other T2T outcomes, including MDA and VLDA.[36]

All the mentioned scores are only surrogates for the hard endpoints, which mainly include radiographic damage and long-term disability and represent the ultimate goal of any therapy in PsA.[11] However, these hard endpoints are slow to achieve and their inclusion in a T2T strategy, where timely interventions are needed, remains challenging.

Table 2: Composite measures used in psoriatic arthritis.

	Peripheral involvement				Global assessment			Inflammation	Function and HRQOL	Skin involvement	Axial involvement
	TJC	SJC	Enthesitis	Dactylitis	Pain VAS	PtGA	PGA	ESR/CRP	HAQ	PASI/BSA	Axial
ACR	√	√			√	√	√	√	√		
AMDF	√	√			Joint VAS		√		√	√	
CPDAI	√	√	√	√					√	√	√
DAPSA	√	√			√	√		√			
DAS-28	√	√				√		√			
GRACE	√	√			√ + Joint VAS	√			√ + PsAQOL	√	
MDA	√	√	√		√	√			√	√	
VLDA											
PASDAS	√	√	√	√		√	√	√	SF-36		
PsARC	√	√				√	√				
RAPID3					√	√			√		

Grey boxes indicate that the composite measure does not include the corresponding item.

ACR: American College of Rheumatology; AMDF: Arithmetic mean Desirability Function composite score; BSA: body surface area; CRP: C-reactive protein; CPDAI: Composite Psoriatic Disease Activity Index; DAPSA: Disease Activity in Psoriatic Arthritis; DAS-28: Disease Activity Score 28 joints; ESR: erythrocyte sedimentation rate; GRACE: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis Composite Index; HAQ: Health Assessment Questionnaire; HRQOL: Health-Related Quality of Life; MDA: minimal disease activity; PASDAS: Psoriatic Arthritis Disease Activity Score; PASI: Psoriasis Area Severity Index; PGA: Physician Global Assessment; PsARC: Psoriatic Arthritis Response Criteria; PtGA: Patient Global Assessment; RAPID3: Routine Assessment of Patient Index Data 3; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale; VLDA: very low disease activity.

Table 3: MDA criteria and DAPSA are the most recommended outcome measures in psoriatic arthritis.

Outcome measure in PsA	Calculation
MDA	
Tender joint count ≤1 (out of 68 assessed) Swollen joint count ≤1 (out of 66 assessed) PASI ≤1 or BSA ≤3% Patient's assessment of pain (VAS) ≤15 Patients' global assessment of disease activity (VAS) ≤20 HAQ-DI ≤0.5 Tender entheseal points ≤1	A patient is classified as in MDA when they meet 5 of the 7 criteria. A patient is classified in VLDA when they meet all 7 criteria.
DAPSA	
Tender joint count (out of 68 assessed) Swollen joint count (out of 66 assessed) CRP (mf/dL) Patient's assessment of disease activity (NS 0–10) Patient's assessment of pain (NS 0–10)	DAPSA score is the sum of all the above. 0–4 remission, 5–14 low, 15–28 moderate, >28 high disease activity.

BSA: body surface area; DAPSA: Disease Activity in Psoriatic Arthritis; HAQ-DI: Health Assessment Questionnaire Disability Index; MDA: minimal disease activity; NS: numerical scale; PASI: Psoriasis Area Severity Index; VAS: visual analogue scale; VLDA: very low disease activity.

Beyond the discussed endpoints, EMMs are also essential to address. The prevalence of common EMMs in PsA is 90% for psoriasis, 3–7% for inflammatory bowel diseases, and 1–3% for uveitis.[37,38] They should be identified and managed in a multidisciplinary setting as their presence may significantly impact the treatment decision.

Finally, the choice of the target of the disease activity should take comorbidities, patient factors, and drug-related risks into account.[11]

Is there a choice of several effective available therapies that allow the clinical target to be reached?

The choice of therapies for PsA has tremendously increased during the last decade. Several effective therapies are now approved, and many others are under study (Table 4).

According to the EULAR, ACR/NPF, and GRAPPA recommendations,[12,13,22] conventional synthetic disease-modifying drugs (cs-DMARDs, usually methotrexate) can be used after the failure of non-steroidal anti-inflammatory drugs (NSAIDs), except when axial disease and/or enthesitis are predominant. After the failure of cs-DMARDs, the biologic therapies (anti-TNFα, anti-IL-12/IL-23, anti-IL-17A) and the small molecules (JAK inhibitors, phosphodiesterase type 4 inhibitors) are recommended. They should be prioritised according to the main domain involved and several treatment algorithms were proposed by the international, regional, and local recommendations. More recent data regarding anti-IL23-p19 seem to be very promising, expanding the therapeutic armamentarium furthermore.[39-41]

Is the endpoint supported by findings from RCTs suggesting that early aggressive treatment approaches would be advantageous?

Evidence of the effectiveness of the T2T strategy was assessed in PsA in a key trial, the TICOPA study,[32] published in 2015.

TICOPA was an open-label study conducted in the UK and included 206 patients who were DMARD-naïve and had a PsA of short duration (<2 years). The study duration was 48 weeks.

Table 4: Effective therapies in psoriatic arthritis, axial spondyloarthritis, and extra-musculoskeletal manifestations.

	Psoriatic arthritis	axSpA	Psoriasis	Crohn's disease	Ulcerative rectocolitis	Uveitis
TNFα inhibitors	++	++	++	++ (except etanercept, golimumab)	++ (except etanercept, certolizumab)	++ (adalimumab, infliximab)
IL-17A inhibitors	++	++ (secukinumab, ixekizumab)	++	--	--	?
IL-12/ IL-23 inhibitors	++	-	++	++	+	?
IL23 inhibitors	+	-	++	+	+	?
JAK inhibitors	++	+	+	+	++	?
PDE4 inhibitors	++	-	++	?	+	?

++	FDA-approved
+	Peliminary data on clinical efficacy
?	Not studied/insufficient data
-	Failed to meet primary endpoint
--	Disease-aggravating effect

axSpA: axial spondyloarthritis; FDA: U.S. Food and Drug Administration; PDE4: phosphodiesterase 4.

The patients were randomised to either standard therapy with 3-monthly evaluations with no strict guidance about the treatment decisions, or tight control (TC) with 4-weekly evaluations and step-up therapy (starting with methotrexate and stepping-up to adalimumab) if MDA was not reached. At Week 12, MDA was achieved in 24% of the TC group. The proportion of patients reaching ACR20, ACR50, ACR70, and PASI75 was significantly higher in the TC group. Moreover, a significantly greater improvement was observed for patient-reported outcomes in the TC arm. Regarding the treatments, the use of biologics was much higher in the TC group, and this group had a much higher incidence of adverse events.

Regarding radiographic progression, although it was numerically lower in the TC group, it did not reach statistical significance at Week 48. It was argued that the included population had mild disease with low baseline radiographic scores and consequently a low risk for radiographic progression.[42]

Other studies where therapy was altered based on achieving a target were conducted with anti-TNF clinical trials.[24] They included a plan in the study protocol for an escalation of treatment if pre-specified targets were not met, labeled as an 'early escape' arm where patients at a set time point (12 or 16 weeks), still in the double-blind portion of the study, could be re-randomised to potentially increase therapy if a particular reduction in their disease activity was not met. The target used in these studies was the reduction in the number of tender and swollen joints, which is a questionable endpoint. Moreover, these studies were not investigating the impact of T2T in a robust comparison against standard care.

Therefore, there is a clear need for additional RCTs that investigate the value of T2T strategies in PsA. Moreover, evidence on the effect of these strategies on the long-term outcomes, namely radiographic damage, function, and health-related quality of life, is essential.

Is the strategy cost-effective?

An analysis from the TICOPA study[32] from the perspective of the UK National Health System (NHS) found that when this strategy was applied in a nation-wide sample, the incremental cost-effective ratio was 54,000 GBP (70,200 USD) per quality-adjusted life year (QALY), which exceeded the threshold allowable by the NHS and drove the authors to conclude that T2T strategy in PsA was not cost-effective.[43] The analysis did not incorporate indirect costs to patients, such as productivity loss; incorporating such costs likely would make tight control even less favourable due to its expense.

Is the T2T strategy acceptable by the stakeholders?

The T2T concept was adopted by the 2018 GRAPPA recommendations for the use of composite measures and treatment targets in PsA,[23] the ACR 2018,[13] and the EULAR 2020 PsA management recommendations.[12] The ACR gave only a conditional recommendation for the use of the T2T strategy over not following a T2T strategy, and stated that one might consider not using a T2T strategy in patients in whom there are concerns related to increased adverse events, costs of therapy, and patient burden of medications associated with tighter control. The latest EULAR recommendations updated in 2020 rephrased their T2T recommendation. They specified that the target should be remission or low disease activity (instead of minimal disease activity), while acknowledging the difficulty of defining remission and suggesting using the abrogation of inflammation as an indicator of remission. They gave this recommendation a Grade A, with a high level of agreement (9.4).

When considering whether T2T is applied in practice, studies showed that it was adopted by only a minority of patients.[44] From the patients' perspective, they may have adapted to their disease and became reluctant to change if they feel 'OK' even if they still have some disease activity. Also, they might disagree with the physician's measure of their disease activity. Furthermore, some patients who are required to make out-of-pocket contributions to healthcare might be unwilling to visit their rheumatologist more frequently.[1]

Regarding the HCPs, a GRAPPA survey showed that 56% reported that they do T2T in clinical practice.[23] Also, a qualitative study of clinicians' perspectives identified the barriers to implementation of T2T in PsA using interviews with rheumatologists and other healthcare professionals:[45] individual motivation to change clinical practice, lack of consensus on what to measure, what is achievable with limited resources, and mandatory versus voluntary pressures to change. Moreover, T2T requires frequent visits and the use of standardised outcomes measures, which may be challenging for rheumatologists with busy practices.[1]

Axial Spondyloarthritis

Is there a proactive, clear endpoint, which is the aim of the treatment?

For the first time in the history of SpA research, evidence has been accrued to suggest the value of 'targeting disease activity' because disease activity leads to new syndesmophytes in patients with axSpA.[17,18]

Many endpoints were proposed in T2T strategies in axSpA: from markers of disease activity (C-reactive protein [CRP], Bath Ankylosing Spondylitis Activity Index [BASDAI],[46] Ankylosing Spondylitis Disease Activity Score [ASDAS],[47-49] Assessment of Spondyloarthritis International Association [ASAS] Remission); [50] to markers of structural progression, disability (ASAS Health Index; ASAS-HI),[51] as well as comorbidities (smoking cessation, NSAID intake, hypertension, diabetes).

Also, these include EMM and sequelae of the long-standing disease, such as cardiovascular disease and osteoporosis.

The two most-used target measures for axSpA in clinical practice are the BASDAI and the ASDAS (Table 5).[52]

The ASDAS was developed to attempt to overcome some of the limitations of the BASDAI. Indeed, due to the subjectivity of the items included on the BASDAI, there is often discordance between patient and clinician assessments of the disease activity.[53] ASDAS includes some questions from the BASDAI as well as patient and physical global assessments and laboratory measures (either the CRP or the erythrocyte sedimentation rate [ESR]).

Table 5: Bath Ankylosing Spondylitis Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) are the most recommended outcome measures in axial spondyloarthritis.

Outcome measure in axSpA	Calculation
BASDAI	
1. How would you describe the overall level of fatigue/ tiredness you have experienced? 2. How would you describe the overall level of ankylosing spondylitis neck, Back, or hip pain you have had? 3. How would you describe the overall level of pain/swelling in joints other than neck, back, or hips you have had? 4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure? 5. How would you describe the overall level of morning stiffness you have had from the time you wake up? 6. How long does your morning stiffness last from the time you wake up?	Assess each question on a NRS of 0 (none) to 10 (very severe); alternatively, a VAS can be used for questions 1–5 (NRS preferred by ASAS) Calculation of BASDAI: • Compute the mean of questions 5 and 6. • Calculate the sum of the values of questions 1–4 and add the result to the mean of questions 5 and 6. • Divide the result by 5. A BASDAI score ≥4/10 is considered as the threshold above which a disease status can be considered as 'active'. A change of at least 50% in the BASDAI is usually considered as reflecting a clinically relevant improvement
ASDAS inactive disease	
1. How would you describe the overall level of AS neck, back, or hip pain you have had? 2. How active was your spondylitis on average? 3. How would you describe the overall level of pain/swelling in joints other than neck, back, or hips you have had? 4. How long does your morning stiffness last from the time you wake up? 5. CRP measured in mg/L or ESR	ASDAS-CRP = 0.121 x total back pain + 0.110 x patient global + 0.073 x peripheral pain/swelling + 0.058 x duration of morning stiffness + 0.579xln(CRP+1); ASDAS-ESR = 0.113 x patient global + 0.293 x √ESR + 0.086 x peripheral pain/swelling + 0.069 x duration of morning stiffness + 0.079 x total back pain Assess each question on an NRS of 0 (none) to 10 (very severe) ASDAS inactive disease is <1.3
ASAS partial remission	
A value not above two units on a 0–10 scale in four of four ASAS domains 1. Physical function (BASFI) 2. Pain (by VAS) 3. Inflammation (morning stiffness) 4. Patient global assessment (by VAS)	

ASAS: Assessments of Spondyloarthritis International Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NRS: numerical rating scale; VAS: visual analogue scale.

However, the ASDAS has some limitations: it does not incorporate other objective measures of inflammation, such as those found on imaging. ASDAS has validated thresholds for disease activity categories, whereas BASDAI does not, and it is the preferred measure in axSpA according to T2T international task force recommendations.[11]

Recent studies showed that achievement of an inactive disease status (ASDAS 1.3) while on treatment with anti-TNFα resulted in almost complete radiographic spinal progression inhibition during the following 2-year radiographic interval.[16,19] Other anti-TNFα trials showed that 15–35% of patients reach ASDAS-Inactive Disease (ASAS-ID).[20,21] ASAS partial remission can be used, but its main limitation is that it relies partly on the Bath Ankylosing Spondylitis Functional Index (BASFI), and a patient with irreversible structural damage may be unable to fulfill ASAS partial remission criteria.[54] ASDAS low disease activity can also be a therapeutic target,[11,16] but it is still debated because of the lack of data.[52]

In response to the lack of a definition of AS disease severity, ASAS developed an instrument based on the International Classification of Functioning, Disability, and Health (ICF) model of function and health, the ASAS-HI.[51] A value ≥12.0 serves as the cut-off between poor and moderate health, whereas a value <5.0 is the cut-off between good and moderate health. The ASAS-HI serves as the primary outcome measure in a recent T2T trial in axSpA.[55]

As for the structural damage evaluation, it could be performed by sacroiliac and spine radiographs and also by MRI. Some have proposed that imaging could be used in patients in clinical remission in whom tapering of biologics is considered.[2] However, this suggestion was refuted by Smolen et al.[11] because there are no data justifying the use of imaging in follow-up yet, and it is not feasible to perform MRI repeatedly in axSpA.

Less-conventional outcomes, such as smoking cessation, NSAID use, and cardiovascular disease, require a long follow-up time and are therefore not easy to assess in RCTs but can be assessed in prospective cohort studies.[2] However, such information would be relevant to understand the effects of treatment on long-term complications of axSpA and to optimise the T2T approach, especially in cases where access to different biotherapies is not simple.

As mentioned earlier, the choice of the target and of the disease activity should take comorbidities, patient factors, and drug-related risks into account.[11]

As for the EMMs, according to a meta-analysis, the pooled lifetime prevalence of common EMMs in patients with axSpA were 26% for uveitis, 9% for psoriasis, and 7% for inflammatory bowel disease.[56] They should also be evaluated using a multidisciplinary approach.

Is there a choice of several effective, available therapies that allow the clinical target to be reached?

As with PsA, the choice of therapies for axSpa has increased considerably over the past decade and several effective therapies are now approved (Table 3).

According to the EULAR-ASAS[14] and the ACR[15] recommendations, after NSAIDs failure, the biologic therapies (anti-TNFα, anti-IL-17A) are recommended. They should be prioritised according to the main domain involved, and several treatment algorithms were proposed by the international recommendations. Data from several retrospective observational studies analysis suggested that anti-TNF therapy can delay the radiographic progression in the long term.[19,57,58] Additionally, tofacitinib, a JAK inhibitor, has shown promising results, adding to the armamentarium of the treatment of axSpA.[59]

Is the endpoint supported by findings from RCTs suggesting that early aggressive treatment approaches would be advantageous?

To date, there have been two T2T trials in axSpA.

The STRIKE study[60] was a German RCT of patients with axSpA meeting the ASAS axSpA criteria and having been symptomatic for <5 years, who were randomised to T2T versus usual care. In the T2T arm they were assessed monthly, and the protocol involved starting with an NSAID and escalating to adalimumab. The primary outcome was ASDAS inactive disease (ASDAS-ID) at 32 weeks. Unfortunately, this trial was stopped due to slow recruitment.[52]

TICOSPA[55] is a European pragmatic, prospective, cluster-randomised controlled trial of patients with axSpA, comparing tight control with monthly assessments to usual care for one year. The primary outcome is change in the ASAS-HI over 1 year. Secondary outcome measures include ASDAS, BASDAI, quality of life, and resource

utilisation. The strategy was pre-specifed by the scientific committee based on current axSpA recommendations and aiming at a target of ASDAS <2.1, with visits every 4 weeks. The treatment decisions in usual care arms were at the rheumatologists' discretion, with visits every 12 weeks. One hundred and sixty patients were included (80 in TC and 80 in usual care). The mean age was 37.9 (±11.0) years with a disease duration of 3.7 (±6.2) years. 51.2% were males. Radiographic damage of the sacroiliac joints, an (ever) positive MRI sacroiliitis, and HLA-B27+ were seen in 46.9%, 81.9%, and 75.0% of patients, respectively. Mean ASDAS at inclusion was 3.0 (±0.7) and mean ASAS-HI was 8.6 (±3.7). Although 47.3% versus 36.1% patients in the TC and usual care arms achieved an improvement in ASAS-HI at the 1-year visit, which was considered clinically relevant, the difference was not statistically significant. Across all other outcomes, a trend was observed in favor of the TC arm. The number of biological DMARDs was significantly higher in the T2T arm (56.2% versus 27.2%). The number of infections was comparable in both groups (15 versus 16 in the TC and usual care arms, respectively).

Is the strategy cost-effective?

To date, there is one cost-effectiveness analysis of T2T strategies in axSpA. Indeed, an analysis from the TICOSPA study found that when this strategy was applied, the T2T strategy was cost-effective with an incremental cost-effective ratio of 19,430 EUR. From a societal perspective, T2T resulted in an additional 0.04 QALY and saved 265 EUR when compared to usual care and a 67% probability of being cost-effective at a cost-effectiveness threshold of 20,000 EUR per QALY.[55]

Is the strategy acceptable by the stakeholders?

Smolen et al.[11] indicated that with T2T strategies, all the options were acceptable; namely, to be left as they had been initially constructed, amended, deleted, or expanded in number and/or changed in sequence. But the lack of evidence available led some societies, such as ACR, not to recommended T2T strategies in axSpA.

Indeed, the ACR 2019 conditionally recommended the regular-interval use and monitoring of a validated AS disease activity measure, and conditionally recommended regular-interval use and monitoring of CRP concentrations or ESR over usual care without regular CRP or ESR monitoring.

For adults with active AS or non-radiographic axSpA, they conditionally recommended against using a T2T strategy using a target of ASDAS <1.3 (or 2.1) over a treatment strategy based on physician assessment. For patients and providers, the panel felt that more convincing evidence of benefit should be present before approving this change in practice. Their rationale was that they feared that choosing a specific target would lead to rapid cycling of all currently available treatments in some patients. That said, they emphasised the importance of having targets in the management of patients.[61]

The EULAR/ASAS 2016 recommendations recommended that a target should be defined and documented, but, unlike the T2T international task force and the ACR guidelines,[11,61] refrained from mentioning the content of such target. This target may change depending on the phase of the disease and the treatments already used previously.

DISCUSSION

Based on the currently available literature, the conditions for applying the T2T in PsA and axSpA are partially met.

First, proactive outcome measures are available, however, there is no clear consensus regarding the choice of the optimal measure. Using a universal target allows for better comparability between the clinical trials. Moreover, soft endpoints should be validated against a gold-standard hard endpoint (such as long-term disability, quality of life measures, and/or radiographic damage). DAPSA and MDA in PsA and ASDAS in axSpA should be correlated with radiographic scores and long-term measures of disability to properly estimate the effect of a treatment strategy on the general burden of the disease, respectively. Acceptable cut-off scores for soft outcomes, in relationship to these hard outcomes, should be adopted on larger scales. Furthermore, the inclusion of radiologic measures and

clinical activity related to EMMs in T2T studies should be discussed but may require longer follow-up studies.

Second, there is a choice of several available therapies for both diseases, and the treatment armamentarium is constantly increasing.

Third, additional RCTs demonstrating the effectiveness of a T2T approach in providing an advantage over the standard care are still needed. Researchers should continue to evaluate whether current therapeutic tools are sufficient to reach the proposed targets and investigate the benefit from the active implementation of non-pharmacological treatments in the T2T strategies.

Fourth, cost-effectiveness studies are needed and should include patients from different healthcare systems. Also, the inclusion of non-pharmacological treatments, particularly in settings of low economic resources, should be considered.

Fifth, the implementation of T2T recommendations in routine care and the adherence to its application in clinical practice should be promoted.[62,63] Financial constraints, staff shortages, patients' reluctance, and high clinic demands are among the reasons for implementation difficulties. Many methods are available to implement T2T in clinical practice. They rank from the least to the most effective: education, rules and policies, reminders and checklists, simplification and standardisation, and forcing functions.[2] T2T may also be successfully implemented if rheumatologists are required to enter detailed data into registries.[64] Moreover, the role of non-physician HCPs such as rheumatology nurses in the implementation of T2T in clinical practice should be evaluated, following very successful experience in diabetes, hypertension, and hyperlipidaemia.[65,66] Furthermore, the role of electronic health records that prompt rheumatologists about escalation/de-escalation opportunities and capture their medical decision-making could allow the development of refined T2T care strategies and deserves further evaluation.[67]

CONCLUSION

In summary, T2T is an emerging management strategy in PsA and axSpA. Preliminary data suggest that a T2T approach might be beneficial to patients with PsA and axSpA. However, further studies are needed to meet all the required criteria before strongly advocating for T2T strategies in clinical practice.

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A Worthwhile Measurement of Early Vigilance and Therapeutic Monitor in Axial Spondyloarthritis: A Literature Review of Quantitative Sacroiliac Scintigraphy

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Abstract

Background: Back pain a common cause for hospital visits. Nuclear skeletal scintigraphy, at a high sensitivity, provides a functional imaging for detecting bone diseases. Sacroiliitis is an inflammation of the sacroiliac joint. Bone scan with quantitative sacroiliac scintigraphy (QSS) has been a useful inflammation indicator for sacroiliac joints. However, QSS has been ignored in the rehabilitation practice.

Objective: To present the background, mechanisms, and current clinical applications of bone scan with QSS in spondyloarthropathy (SpA).

Methods: The authors performed a literature review of QSS through database searching of MEDLINE, Embase, CINAHL, HaPI, Cochrane Review, and citation mining. Studies were included if they had QSS in the methodology performed in adult patients with various diseases. Any articles, including the authors', that can be performed in a clinical setting were enrolled. Articles explicitly referencing QSS were retained for screening.

Results: QSS appearance of SpA, including ankylosing spondylitis, may give rise to early detection. The specificity of sacroiliitis based on QSS increases from 73% to 97%. After investigating the relationship between serum C-reactive protein and sacroiliac joint inflammation in patients with SpA, there appeared to be a significant difference between serum C-reactive protein in serum and in sacroiliac ratio (particularly the middle part of the both joints), indicating a systemic inflammatory response to flair-up of SpA, for example, serum C-reactive protein as an indicator of inflammation. Sacroiliitis also occurs in post-streptococcal reactive arthritis. The involvement of sacroiliac joints in the development of post-streptococcal reactive arthritis had been demonstrated a significant correlation between anti-streptolysin O titres and QSS in patients with post-streptococcal reactive arthritis. Lower extremity periostitis acts as a human model in the study of bottom-up processing for periostitis-induced sacroiliac pain. The use of QSS can also monitor sacroiliac joint dysfunction before and after laser therapy. Improvements of the sacroiliac joint after convalescing of foot periostitis have been reported.

Conclusions: Bone scan using QSS is a good screening measurement in scintigraphy rehabilitation for early detection of SpA and raises awareness of physicians toward the next step of diagnosis.

INTRODUCTION

Back pain is a common cause for hospital visits. The pain origins for these patients can be determined using various methods. MRI and nuclear skeletal scintigraphy are clinical tools to determine certain aetiologies contributing to back pain. MRI is the first choice for examination over the past four to five decades. MRI produces precision images of bone and soft tissues in 3D displays. MRI is, nevertheless, not a good diagnostic tool for bone surveying and the procedure is time-consuming, costly, and has contraindications, for example the presence of cerebral aneurysm clips, cardiac pacemakers, and cochlear implants.[1] Breathing movements during MRI can lead to distorted images.[2] MRI produces images of specific body regions, and poor cortical bone details with only 70% sensitivity in detecting areas of active inflammation prior to the development of structural lesions.[1,3]

In contrast to CT or MRI, nuclear skeletal scintigraphy provides functional imaging for bones of the entire body at a reasonable cost, as well as high sensitivity for various bone diseases despite of a lower resolution of the bone scan. Such bone scans are the most widely used method to diagnose bone diseases and being critical in monitoring bone metastases.[4,5] This may be posed as, in analogy, CT/MRI sees individual trees but not the forest, and nuclear medicine sees the forest but not individual trees.

Seronegative spondyloarthrithis (SpA) is closely associated with back pain and its early diagnosis is crucial. Sacroiliitis being the earlier symptom is, therefore, an important condition. Physicians, especially those of rheumatology and rehabilitation, typically diagnose SpA based on the international standards, like the Amor and Assessment of Spondyloarthritis International Society (ASAS) criteria. In the Amor criteria, 13 criteria are used to classify SpA with no image evidence.[6] The diagnosis of SpA has been modified in several versions from 1990 to 2016.[6-16] Before the start of SpA treatment, sacroiliitis could be caused by other diseases like psoriatic arthritis, Reiter's syndrome, reactive arthritis, inflammatory bowel disease, or those that are inflammatory bowel disease related. These other causes need to be excluded first.[17] Scientists have developed deep learning-based algorithms that can be use to detect sacroiliitis and grade

the classification of SpA on plain radiograph with high sensitivity and accuracy.[18,19] These approaches have overcome the interobserver variability in image interpretation. However, a group of researchers reported that technetium 99m-methyl diphosphonate (Tc-99m MDP) bone scan is more useful than plain radiographs in the early detection of SpA after study of 136 sacroiliac (SI) joints (42 patients and 26 controls) for 1 year and concluded that some patients (n=2) with negative findings from plain radiograph and MRI showed positive results in a bone scan.[20]

Clinicians often accentuate on the uncomfortable or tender region pointed out by the patient. Nuclear skeletal scintigraphy is an alternative method to determine the exact location of discomfort. There are four common types of scans: whole body bone scan,[21] three-phase bone scan,[22] single photon emission CT (single photon emission CT [SPECT]),[23] and quantitative SI scintigraphy (QSS).[24] These four scans all use the same radiotracer, Tc-99m MDP, which can be taken up by human skeleton. SPECT along or combined with CT as hybrid imaging can detect the exact location of neck pain in facet joint disorder,[25] and raise the alarm of the sternoclavicular joint inflammation during flare-up in psoriatic arthritis.[26]

Although other radiotracers, such as Tc-99m-pyrophosphat, or Tc-99m hydroxymethylene diphosphonate, can be used instead, doctors of nuclear medicine still prefer Tc-99m-MDP as the choice of radiological compound.[27] Tc-99m MDP is typically delivered in the bloodstream by an intravenous injection to disseminate in the body before being deposited in the bone. The primary mechanism of detecting bone lesions based on Tc-99m MDP is an abnormal accumulation due to osteogenic activity on the bone surface secondary to the calcium uptake in the affected area. Nuclear medicine bone scans can also present as a photopenic or cold zone in some bone lesions, such as the condition of bone necrosis, severe bone damage-like trauma, or tumour cell invasions leading to ischaemic changes.[28,29]

In this paper, the authors reviewed an alternative strategy: nuclear medicine bone scan with QSS to approach a patient with a comprehensive check-up in rehabilitation practice.

METHODS

To examine clinical application of QSS, the authors developed a search strategy of QSS using a literature review through database of MEDLINE, Embase (Ovid), CINAHL (EBSCOhost), HaPI (Ovid), Cochrane Review (Ovid), and citation mining. The research was not limited to articles published in English because abstracts in English were available. Studies were included if those had QSS in methodology performed in adult patients with various diseases. Any articles, including the authors', that can be performed in a clinical setting were enrolled. Articles explicitly referencing QSS were retained for screening. The searches were conducted on 3rd May 2017 and updated on 31st March 2021. Summarised here are the most relevant aspects of the studies of SpA and different diagnoses of SpA according to different clinical imaging, and a critical discussion on the potential advantages and disadvantages of QSS.

RESULTS

Quantitative Sacroiliac Scintigraphy Is an Easier Way to Approach Sacroiliitis Compared to Unspecified Physical Examination

Sacroiliitis is an inflammation of the SI joint as the result of systemic diseases or stress (e.g., abnormal shearing force). The inflammation in the SI joint is also seen in individuals without SpA, including postpartum females, recreational runners, military recruits, professional ice hockey players, and healthy controls with or without symptomatic back pain.[30-33] A substantial portion of those people displayed sacroiliitis and bone marrow oedema on MRI at baseline.[31,32,34,35] Those structural lesions without the development of fat metaplasia have shown a more mechanical than inflammatory origin.[34] In addition, the CT Syndesmophyte Score (CTSS), SI joints scores, and MRI lesions were not significantly increased in those people after a period of time, which indicated that stress may also cause sacroiliitis.[31,33,34,36]

Clinical manifestations of sacroiliitis are lower back pain, inguinal ligament pain, or buttocks pain, and even radiated pain to hamstrings similar to sciatica.[37]

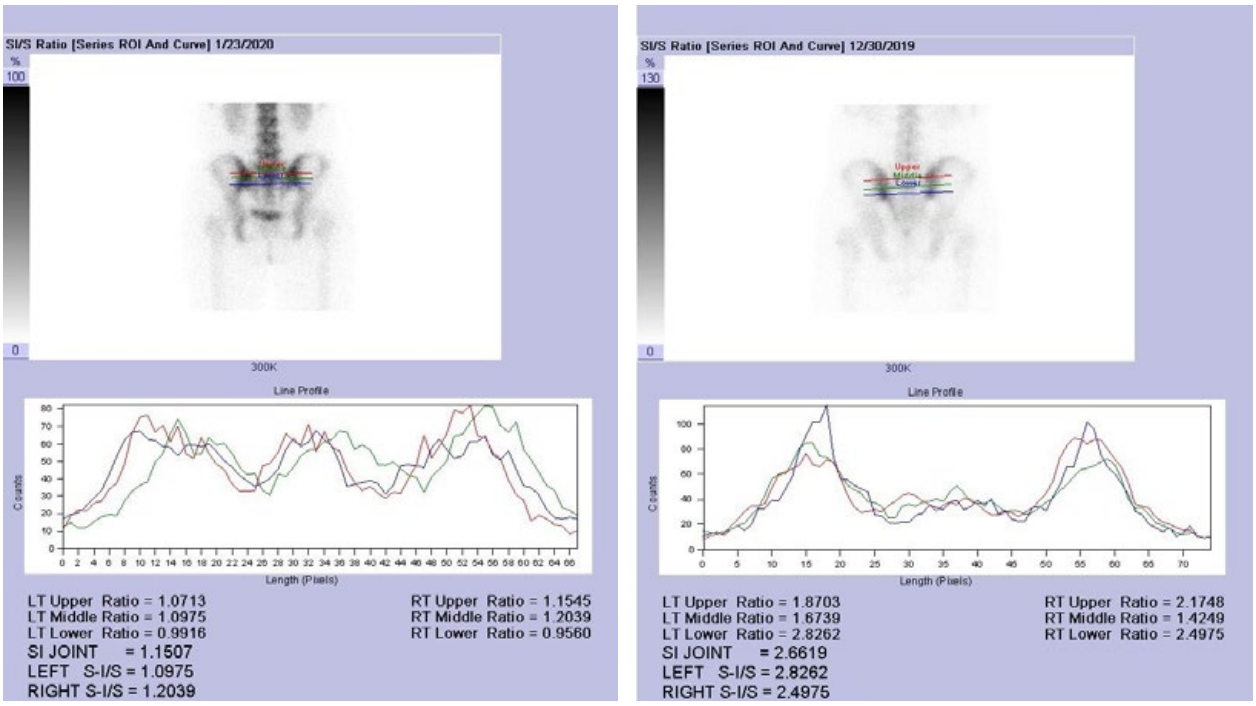

Figure 1: Methods used to obtain a quantitative sacroiliac joint-to-sacrum ratio.

From the ROI based on accountable images, the ratio is obtained after measuring total number of counts within the region of SI joint and divided by total number of counts within an equal-size region at the sacrum. The ratio for the upper (red), middle (green), and lower (blue) parts of both joints can be measured individually.

Left panel: a subject with normal SI joint. **Right panel:** a patient with AS.

AS: ankylosing spondylitis; ROI: region of interest; SI/S: quantitative sacroiliac joint-to-sacrum ratio.

The Fortin finger test may indicate the area potentially generating the pain by asking patient to point at the area of pain to the clinician.[38] Those patients who fail to point out their painful areas would be identified to have poor outcome of their disease. Patrick's test is another method of physical examination for sacroiliitis. In this method, the examiner stretches the patient's SI joints according to the following motions: flexion, abduction, and external rotation of the hip joint.[39] A positive test result is one in which refers to back pain or buttock pain, whereas groin pain is a sign that is more indicative of sacroiliitis.[39] In addition, Gaenslen's sign is a test of sacroiliitis by abducting one side of hip joint and extending the other side in counter-rotation.[40] The result is same as in the Patrick's test.[40] Another test for sacroiliitis is the posterior superior iliac spines (PSIS) distraction test.[41] A positive result is feeling pain when a medial-to-lateral direction force is applied on PSIS.[41] In brief, there are many methods to test for sacroiliitis, but all with low specificity.[42]

Nuclear medicine bone scan with QSS has been a useful inflammation indicator for SI joint for the last 50 years. QSS is typically done following an intravenous injection of about 750 MBq Tc-99m MDP. Planar imaging of the spine and SI joints achieves in the antero-posterior projections 3–4 hours after the injection, using a gamma camera via an elliptical course (360°, 64 projections, 20 sec/projection) the camera acquires images around the SI joints, storing in 128x128 matrices. Using the region-of-interest (ROI) method, a quantitative SI joint-to-sacrum ratio (or SI ratio), is computed based on counts at similar regions measured at the SI joint and at the sacrum.[43] The ratio for the upper, middle, and lower parts of both joints is measured individually (Figure 1). In brief, the inflammation is considered as negative if the ratio is <1.3, or equivocal if around 1.4, or positive if >1.5.

In 1977, Buell et al.[44] were the first to report higher SI ratios in patients with SI disease. In 1998, Kaçar et al.[45] reported that for subjects

20 to 60 years old, the normal ranges of counts of SI joint versus over counts of sacrum ROI were between 0.74 and 1.22 for females, and between 0.87 and 1.31 for males. The reference SI ratios were estimated to be an average of <1.3200 for normal subjects and <1.3812 for late arthritic patients, while even higher at 1.5200–2.0900 for those with early arthritis. It was reported that patients with radiographic Grade I–II were considered to have early arthritis and patients with radiographic Grade III–IV were considered to have late arthritis.[45] Tiwari et al.[46] later showed four quantification methods of the SI joint index: irregular ROI, rectangular ROI, profile peak counts, and profile-integrated counts. All of these methods gave similar results. Sebastjanowicz et al.[47] reported a range of SI ratio between 1.18 and 2.28 for control subjects, with the highest standard deviation in paediatric patients. Therefore, SI ratio is a good measure for detecting early but not late arthritis.[45] The maximum and minimum of SI values need to be considered for younger (<20 years old) and older patients (>61 years old).[47] SI ratios can be measured individually as the upper, middle, and lower third due to distinct anatomic structures and kinetic physiology in the three parts of the joint on the bilateral sides.[48]

Unlike adults,[49,50] children's quantitative SI indices may give good results using L5 as the background[51] or with the use of MRI because these younger subjects have more synovial enhancement without bone marrow oedema.[52]

The earlier study regarding QSS in healthy people was performed in a medical centre where a posterior planar film of the pelvis was obtained 3 hours after injection of 740 MBq 99mTc-MDP and the SI ratio was calculated.[53] The results showed that the age-related changes in SI ratio are significant between sexes in certain age groups, but not lateralisation, and the SI ratios dropped steadily with age in females, whereas two plateaus appeared at ages 21 to 40, and 41 to 70 years in males.[53]

DISCUSSION

Quantitative Sacroiliac Scintigraphy for Spondyloarthropathy, Including Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a disease of axial SpA but is often recorded as suspicious by radiologists after a plain X-ray, and is, therefore, sometimes diagnosed late. In the 1980s, SI ratio was being used as important indicator in early vigilance of AS, particularly in males to prevent its progression to sacroiliitis.[49,54-57] Although QSS showed a limited sensitivity and specificity of approximately 50% for each when appropriate controls were used,[58,59] the SI ratio of 1.55 meant that AS disease progression was expected to last <3 years and >3 years at 1.40.[60]

In 1993, Collie et al.[61] measured SI ratios for six of 11 patients (5 female, 6 male), and found elevated ratios (>1.5 for both SI joints) in four of them. After 2 years, two of these patients showed higher SI ratios that preceded plain roentgenologic abnormalities. In two patients, unilateral sacroiliitis on plain radiographs was confirmed as bilateral on QSS. They suggested that the scintigraphic appearance of AS, though not unique to the disease, offers the opportunity for early detection and vigilance, avoiding further unnecessary investigation and treatment for both suspected as well as unsuspecting cases.[61]

In addition, Koç et al.[62] reported that with SI ratios, the specificity of sacroiliitis based on bone scans increases from 73% to 97% and negative predictions increase up to 91%, in parallel with positive predictions. The authors of this current study concluded that with regard to time and cost, bone scan is slightly better than MRI and SPECT/CT in detecting AS and sacroiliitis.[62]

Elevation serum levels of high sensitivity C-reactive protein (hs-CRP) are considered a risk factor/biomarker for various diseases, including SpA. A previous study had retrospectively investigated the relationship between serum hs-CRP and SI joint inflammation in 29 patients with SpA (n=29; mean age: 32.27 years; female–male ratio: 6:23). All patients underwent hs-CRP testing and skeletal scintigraphic scans with QSS between January 2007 and September 2013. The results showed a significant difference between hs-CRP in serum and in SI ratio (particularly

the middle part of SI joint, on both sides). It was concluded that the significantly high concentrations of serum hs-CRP may indicate a systemic inflammatory response to a flair-up of the SI joint and should be an indicator of SI inflammation in SpA.[63]

Although QSS may not be mandatory for most patients with suspected AS, an empirical practice has depicted that it has a role in selected cases where there is a very visible disorder in the absence of obvious roentgenologic changes. For accurate diagnoses of SpA, QSS is only recommended when combined with a CT scan.[64]

The importance of concomitant use of CT in the assessment of SI joints along with scintigraphy includes the following: the combination of semi-quantitative analysis of CT and quantitative analysis of SI joints can increase the unique specification of the risk level for active sacroiliitis;[65] CT is the gold standard for bone erosion and superior to conventional radiography and MRI,[65] it enables the cross-sectional, multi-planar visualisation of the pathologic processes, which was better than conventional radiography,[66-68] in addition, the Modified New York Criteria scoring system for sacroiliitis can also applied to CT; by using spectral CT, fat deposition and bone marrow oedema can be measured similarly to MRI, which can increase the sensitivity for early changes of sacroiliitis;[65,68] and, other than bony erosion and relative water and calcium ratio of the SI joint, CT can detect sclerosis and syndesmophytes, which could be helpful to identify differential diagnoses in chronic changes in sacroiliitis.[65,68]

Quantitative Sacroiliac Scintigraphy for Post-Streptococcal Reactive Arthritis

Titers of anti-streptolysin O (ASLO) are of diagnostic value in the early detection of post-streptococcal reactive arthritis (PSRA),[48,69-71] early arthritis after rheumatic fever,[72-74] and movement disorder.[75] The dividing line is normal if the titer is ≤116 IU/mL, and abnormal if the titer is >116 IU/mL. PSRA is a non-suppurative sequela of a prior streptococcal infection.

In Asia, some scholars have demonstrated the involvement of the SI joint in the development of PSRA. In a study, a total of 84 subjects (mean age: 23.0; range: 18.0–36.4) underwent QSS and their ASLO titers were measured (range: 25–520 IU/mL). The SI joint was divided into three regions: upper, middle, and lower parts. Depending on fibrous cartilage, ligament, and the direction of the SI joint, bilateral QSS measurements of the three parts were collected. A highly significant correlation was found between ASLO titers and SI ratios ($p<0.0001$). An increment of 1 IU/mL of the titer resulted in a significant increment of SI ratio by 0.0008 units. It was also found that with the increased ASLO titer per unit, SI ratio increased significantly by 0.0008 units and thereafter 0.0074 units per additional year.[48] The findings suggested that SI joint involvement is a manifestation of PSRA. The results demonstrated a strong correlation between the ASLO titer and the QSS in patients with PSRA. Subjects with SI joint involvement should be advised to have an ASLO titer measured and a QSS done.[48]

It was noticed that those patient with SI also reported upright postural abnormality. It was, therefore hypothesised that an imbalance of the lumbopelvis due to SI disorder might produce a positional change, and there would be different postural sway when standing upright. All subjects underwent 10 sway tests to assess static sway in an upright standing posture. With eyes open and plantar flexion, the high ASLO group had bigger values in sway area, sway velocity, and sway intensity. The values of sway velocity and intensity obtained with eyes open and plantar flexion and dorsiflexion had lower intensity values when compared with those obtained in closed eyes and plantar flexion and dorsiflexion in the high ASLO group, but not in the low ASLO group. Significant differences were found between the two groups in all sway values under all the tested position conditions. It is speculated that subjects with high levels of streptococcal serology have greater sways on all postural parameters compared to those with low serology. The speculation is consistent with proprioceptive deficits in the SI joint contributing to postural impairments,[76,77] as shown in Figure 2. The use of QSS is the first of its kind to detect active SI joint disorder in the studies of PSRA.

Quantitative Sacroiliac Scintigraphy for Osteitis Condensans Ilii

Osteitis condensans ilii (OCI), first reported in 1926, has symptoms that include axial lower back pain and premature arthritis.

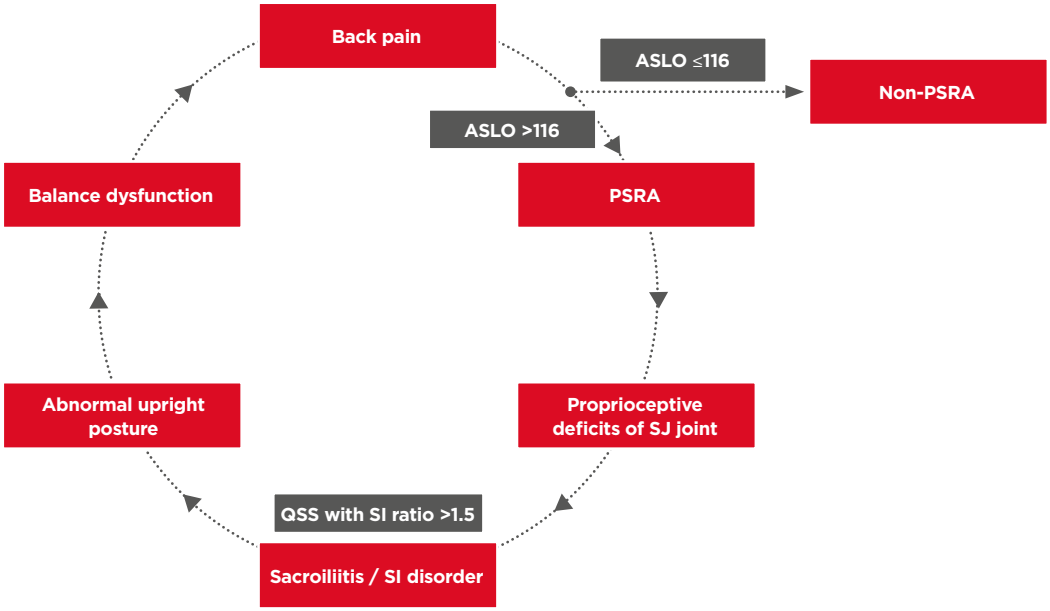

Figure 2: Schematic illustration of the pathophysiology of post-streptococcal reactive arthritis and its related disorders.

ASLO: anti-streptolysin O; PSRA: post-streptococcal reactive arthritis; QSS: quantitative sacroiliac scintigraphy; SI: sacroiliac.

It primarily affects females younger than the age of 40, and often after pregnancy. Parperis K et al. have suggested the term idiopathic pelvis sclerosis might be an alternative term to OCI due to the lack of inflammation evidence in those patients.[78] OCI is considered a diagnosis of exclusion because plain radiograph and MRI findings of the spine were unremarkable;[79] while the characteristic X-ray image may show triangular sclerotic changes in the auricular portion of the bilateral ilium with preserved SI joint space.[80,81] Patients mostly exhibit normal physical and neurological examination but some show SI joint region tenderness and increased lumbar lordosis.[59] From a case-control study, OCI is shown to be associated with pain on SI stress tests. The preserved SI joint space is the key characteristic of OCI.[79] It has been postulated that OCI induces stress on the SI joint, leading to a piriformis muscle syndrome with sciatica. The association between OCI and SI joint stress, and that between sacroiliitis and sciatica, has been reported. It is characterised by a favourable prognosis;[78] therefore, the treatment goal was to improve their health-related quality of life.[78] In clinical practice, symptoms of OCI presented with piriformis muscle syndrome and sciatica could be successfully managed with SI joint injections.[82] The use of QSS is the first of its kind to monitor active SI joint disorder before and after the treatment of OCI. MRI, SPECT, and PET/CT might have the ability to distinguish OCI from other diseases and require larger-scale studies before use in the clinical setting.[81,83,84]

Quantitative Sacroiliac Scintigraphy for Periostitis-Induced Sacroiliac Pain

Juvenile-onset HLA-B27-associated 'unclassifiable' SpA, especially cases without evidence of enteric or genitourinary symptoms, may have tarsal periostitis as an early clinical manifestation and then show bilateral sacroiliac pain later on.[85] One article has reported improvements of the SI joint after convalesce of the foot periostitis, and concluded that stress events, exercise, and abnormal posture can all increase SI ratios, while corrected posture for a period of time, anti-inflammatory drugs, and rehabilitation programmes can all reduce SI ratios.[86]

Periostitis of the lower limbs is a common disorder from sports injuries. Foot periostitis is considered a human model in the study

of bottom-up processing. Calin et al.[87] have demonstrated that pelvic radiography showing fluffy periostitis was equally distributed among symptomatic, asymptomatic HLA-B27-positive, and symptomatic HLA-B27-negative control groups.[87] The diagnosis of foot periostitis, therefore, can be confirmed by medical history and physical examination, as well as triple-phase bone scan using skeletal nuclear scintigraphy. One clinical study[88,89] (n=54) explored functional improvements of the lower limbs after low-level laser therapy (LLLT) with regard to balance function, including postural stability testing and limits of stability. After therapy, there were significant improvements in pain score and balance dysfunction. The study concluded that LLLT is effective for treating lower-limb periostitis and even in short-duration interventions, and LLLT exerted a positive effect on proprioception in these patients.[88,89]

Furthermore, foot pain was hypothesised to induce defective biomechanics and might cause SI joint stress and convalesce of the foot periostitis could restore the abnormal SI joints. The results showed scintigraphic improvements in the SI ratio, indicating significant therapeutic effects on foot periostitis. There was also a significant association between the middle and lower parts of the SI joint. SI ratios for the middle part on both sides were significantly higher (0.06 units) compared to the lower part. In conclusion, the patients with SI joint stress, as the result of bottom-up processing of foot periostitis, could be treated successfully after convalesce of the foot periostitis by either LLLT or conventional treatments.[86] In another report regarding medial tibial stress syndrome (MTSS), similar findings were also reported. Both MTSS and SI joint stress can be confirmed by nuclear scintigraphy.[90]

Outcome measures included the Lower Extremity Functional Scale (LEFS) and QSS. The results showed that after therapy, LEFS was significantly higher (38.45, $p<0.0001$), and QSS was significantly lower ($p<0.0001$). There is also a significant association between the middle and lower parts of the SI joint. It has been confirmed that SI joint stress due to bottom-up processing of MTSS can be normalised after successful therapy of MTSS by LLLT.[90] The use of QSS is the first of its kind to monitor SI joint dysfunction before and after the studies of periostitis-induced sacroiliac pain.

Limitations of Quantitative Sacroiliac Scintigraphy

QSS has several limitations. The first limitation is lower specificity in detecting chronic inflammation. SI values the in acute phase of stress-induced inflammation fall between 1.7 and 1.8 but nearly normal values tend to be reached after 6 months of recovery. The hyper-fixation method for the SI joints may be used in treating chronic SI arthritis. The second limitation is related to the small overlaps in SI indices between lower back pain and sacroiliitis patients and controls.[91] Therefore, the reference values and the cut-off values of SI joints need to be clearly established.[38] In addition to this, stratification of age[27,53,91] and sex[45,53] are needed to distinguish the overlapping area resulted from sacroiliitis. One literature review has included studies about well-defined AS populations only, suspected sacroiliitis, and/or mechanical lower back pain.[92] They excluded the studies without preforming the SI joint–sacrum ratio or giving a clear definition of reference value of the SI joint–sacrum ratio in quantitative scintigraphy and calculating sensitivity or specificity value.[92] They have concluded that although scintigraphy was nearly 50% cheaper and generally more available than MRI, the likelihood ratio of scintigraphy for diagnostic acute sacroiliitis was only between 2.5 and 3.0.[92]

The authors of the review suggested that QSS was limited for diagnostic values for AS diagnosis.[92] Using auxiliary laboratory data and clinical scoring, including serum hs-CRP, vitamin D levels, erythrocyte sedimentation rate, and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), clinicians may able to detect SI inflammation-related diseases from healthy controls.[93] A current article has suggested there is value of QSS in helping the differential diagnoses of back pain-associated conditions, such as suspected fracture,[64] particularly in survivors with SI joint pain after experiencing a vehicle accident.

CONCLUSION

In this article, the authors have revisited skeletal scintigraphy using QSS on patients with SI joint dysfunction, who also present with myalgia, arthritic, or lower back pain. More

than one underlying disorder may contribute to symptoms in these patients. Clinicians need to better understand the pathophysiological mechanisms and the origin of sacroiliitis before prescribing treatments. QSS is helpful in clarifying inflammation of SpA and in disease assessment. In conclusion, the skillful pattern recognition skills of the diagnosis of axial SpA are more important than overdiagnoses by a positive MRI finding. Bone scan using QSS is a good screening and follow-up measurement in scintigraphy rehabilitation for early detection and vigilance of SpA and raises awareness for physicians to adopt the SI ratio in the next steps towards diagnosis.

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The Interplay of Genes with the Gut Microbiota in the Aetiopathogenesis of Spondyloarthropathies and Crohn's Disease: Implications for Future Therapeutic Targets

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Abstract

The phenotypical overlap between the spondyloarthropathies (SpA) and Crohn's disease (CD) has long been recognised. More recently, the co-inheritance of these diseases and the existence of a plethora of shared genetic risk loci have been demonstrated by genealogic databases and genome-wide association studies. Now there is mounting evidence to suggest that the interplay between the gut microbiota and host genetics is central to the shared aetiopathogenesis of SpA and CD. The clinical management of patients with both SpA and CD can be challenging. Preliminary studies seeking to understand this interplay have identified novel therapeutic targets and approaches, which may, in the future, significantly advance patient care. This review provides an overview of the role of host genetics and the intestinal microbiota in the shared aetiopathogenesis of SpA and CD, and explores how this interplay can advance the search for new therapeutic targets.

INTRODUCTION

The spondyloarthropathies (SpA) are a spectrum of inter-related conditions that include axial spondyloarthritis (AxSpA), (also known as ankylosing spondylitis; AS), non-radiographic axial spondyloarthritis, peripheral spondyloathritis (pSpA), reactive arthritis (ReA), and enteropathic arthritis associated with Crohn's disease (CD).[1,2] Phenotypically, AS and CD share many clinical features. Extra-intestinal manifestations of CD include both a peripheral arthritis and a sacroiliitis, which is a hallmark of SpA, whilst AxSpA and pSpA are associated with evidence of microscopic intestinal inflammation on biopsy and capsule endoscopy;[2] one study demonstrating this to be present in 42% of patients with SpA.[3,4] Although this bowel inflammation is considered asymptomatic, it has been shown to strongly correlate with axial disease activity in AxSpA.[3,5,6] Clinical inflammatory bowel disease (IBD) is also common in AxSpA, with a prevalence ranging from 6% to 14% in populations of European decent.[6] The DESIR cohort noted a frequency

of IBD of 2.6% in patients with early AxSpA.[7] Interestingly, in Han Chinese this association is rare at 0.4%, suggesting a genetic and/or environmental difference between these populations.[8] Similarly, SpA features are the most common extra-intestinal manifestations of CD, with approximately 10% of patients with CD developing AxSpA, 13% oligo-articular or poly-articular pSpA, and 5% other typical SpA features such as enthesitis and dactylitis.[9]

The development of classification criteria has enabled better characterisation of these conditions and thus the ability to study overlapping aetiological and therapeutic pathways.[10] However, AxSpA in particular is often a challenging diagnosis to make, with a mean delay in diagnosis from onset of symptoms of 8–10 years.[11]

This review has two main aims: 1) to evaluate the evolving evidence for a shared aetiopathogenesis and, in particular, whether the interplay of host genes and the intestinal microbiota are central to this shared aetiopathogenesis; and 2) to discuss the importance of understanding this interplay in identifying potential new therapeutic targets.

THE SHARED GENETIC ARCHITECTURRE OF SPONDYLOARTHROPATHIES AND CROHN'S DISEASE

The seminal study of Thjodleifsson et al.[12] was the first to provide evidence of the existence of a common genetic background between SpA and CD. In this study of the Icelandic Genealogy Database, first- and second-degree relatives of patients with AS had a 3.1 and 2.0 increased risk of developing CD, respectively, compared to the general population.[12] Near-identical cross-risk ratios for developing AS were found for first- and second-degree relatives of patients with CD.[12]

The estimated heritability of AS by twin studies is >90%,[13] with the Class I major histocompatibility complex (MHC) molecule human leukocyte antigen (HLA)-B27 accounting for much of this risk and representing one of the strongest genetic associations with any common human disease.[14] The prevalence of HLA-B27 is 80–95% in patients of European ancestry with AS, compared with a general population prevalence of 6–16%[14-17] in central and Northern European countries. Interestingly, whilst HLA-B27 is not considered a risk gene for CD, 25–78% of patients with CD who carry this gene will go onto develop AS and another 7–15% will develop an isolated sacroiliitis.[6]

The era of genome-wide association studies (GWAS) has significantly advanced the search for a shared genetic architecture between SpA and CD by identifying a plethora of additional risk loci for these diseases. The risk loci discovered by GWAS have underscored the importance of bacterial detection and handling in the development of both SpA and CD.

An early, watershed study in characterising this shared genetic architecture was Danoy et al.[18] Taking the 53 genetic loci most strongly associated with CD in three separate GWAS, Danoy et al.[18] demonstrated that eight were also significant risk loci for AS, namely *IL23R* (rs11465804), *IL12B* (rs10045431), *CDKAL1* (rs6908425), *LRRK2* (rs11175593), *chr13q14* (rs3764147), *chr1q32* (rs11584383), and *STAT3* (rs6503695, rs744166) (Table 1).[19,20] This constellation of genetic variants highlights the potential importance of the pro-inflammatory IL-23/IL-17 pathway and intestinal microbiota in the shared aetiopathogenesis of CD and SpA. IL-23 expression has been shown to be upregulated in the presence of gut dysbiosis in both the terminal ileum of patients with SpA and patients with CD.[21] Elevated circulating levels of IL-23 lead to the activation of STAT3, which induces the expression of IL23R on the surface of Th17 cells.[22] This receptor enables these pro-inflammatory cells to secrete IL-17 in response to IL-23.[22] Significantly higher levels of IL-17 have been noted in the intestinal mucosa and joints of both patients with SpA and patients with CD compared to healthy controls.[21] Furthermore, in patients with SpA, IL-17 levels have been shown to directly correlate with disease activity (Table 1).[23] In a similar fashion, functional studies have demonstrated that LRRK2 plays an important role maintaining gut and joint homeostasis through the clearance of gut pathogens, such as *Salmonella typhimurium*. This bacterium has been demonstrated to trigger reactive arthritis by causing the activation of the NLRC4 inflammasome in macrophages (Table 1).[24]

Table 1: Genetic susceptibility loci strongly associated with both ankylosing spondylitis and Crohn's disease.

Chr	SNP (type)	MAF* (allele)	Gene†	Function of encoded protein
1	rs11465804 (intronic)	0.034 (G)	*IL23R*	Binds to IL12RB1 to form the IL-23 receptor, which in turn binds IL-23 and mediates stimulation of immune cells via the JAK-STAT signalling pathway
1	rs80174646 (intronic)	0.035 (T)	*IL23R*	
1	rs11584383 (intergenic)	0.154 (C)	*KIF21B*	ATP-dependent motor protein that is highly expressed in CD4+ and CD8+ T cells, natural killer cells, and B cells
2	rs3749171 (missense)	0.151 (T)	*GPR35*	Acts as a receptor for kynurenic acid, an intermediate in the tryptophan metabolic pathway
2	rs35667974 (missense)	0.002 (T)	*IFIH1*	Innate immune receptor that plays a major role in detecting viral infection
2	rs13407913 (intronic)	0.443 (A)	*ADCY3*	Catalyses the formation of the signalling molecule cAMP in response to G-protein signalling
5	rs2910686 (intronic)	0.418 (C)	*ERAP2*	Protease that trims N terminus of antigenic epitopes for presentation by MHC Class I molecules
5	rs10045431 (intronic)	0.151 (A)	*IL12B*	A subunit of cytokine IL-12, which acts on T cells and natural killer cells
6	rs6908425 (intronic)	0.218 (T)	*CDKAL1*	Function unknown
10	rs61839660 (intronic)	0.028 (T)	*IL2RA*	Receptor subunit involved in the regulation of immune tolerance by controlling regulatory T cell activity
10	rs10761648 (intronic)	0.221 (T)	*ZNF365*	Zinc finger protein that may play a role in the repair of DNA damage and maintenance of genome stability

Table 1 continued.

12	rs11175593 (synonymous)	0.050 (T)	*LRRK2*	Serine/threonine protein kinase, which plays a key role in bacterial handling via activation of the NLRC4 inflammasome in macrophages
12	rs3184504 (missense)	0.147 (T)	*SH2B3*	Key negative regulator of cytokine signalling
13	rs3764147 (missense)	0.306 (G)	*LACC1*	Promotes optimal NOD2-induced signalling, cytokine secretion, and bacterial clearance
16	rs26528 (intronic)	0.382 (C)	*IL27*	Heterodimeric cytokine involved in innate immunity
16	rs367569 (intronic)	0.292 (T)	*TNP2*	Involved in replacement of histones to protamine in the elongating spermatids of mammals
17	rs6503695 (intronic)	0.347 (C)	*STAT3*	Regulates differentiation of naive CD4(+) T-cells into Th17 or regulatory T cells
17	rs744166 (intronic)	0.493 (G)	*STAT3*	
19	rs12720356 (missense)	0.028 (C)	*TYK2*	JAK that associates with Type I and II cytokine receptors and promotes cytokine signals by phosphorylating receptor subunits
19	rs679574 (intronic)	0.321 (G)	*FUT2*	Catalyses synthesis of the H antigen on the intestinal mucosa, which provides a carbon source for gut microbiota
19	rs74956615 (3'UTR)	0.014 (G)	*RAVER1*	PTB-binding 1 ribonucleoprotein, which is involved in interferon induction and innate immune response against viruses
20	rs6058869 (intergenic)	0.300 (C)	*DNMT3B*	Required for genome-wide de novo methylation patterns during development

Table 1 continued.

22	rs2266961 (intronic)	0.231 (G)	*UBE2L3*	Catalyses ubiquitination of abnormal proteins enabling early degradation

*Minor allele frequency in the '1,000 Genome' Phase III Combined Population.[20]

†Gene candidate nearest to the index SNP.

cAMP: cyclic adenosine monophosphate; Chr: chromosome; MHC: major histocompatibility complex; SNP: single-nucleotide polymorphism; STAT: signal transducer and activator of transcription proteins.

The association of 1q32 single-nucleotide polymorphism (SNP) rs11584383 with CD and SpA has been independently replicated,[25] but its significance remains to be established. This intergenic SNP is postulated to be in linkage disequilibrium with a functional SNP in a nearby gene.[25] The most likely candidate is Kinesin Family Member 21B (*KIF21B*). This gene is highly expressed in CD4+ and CD8+ T cells, B cells, and natural killer cells.[26] SNPs and copy number variants within *KIF21B* have subsequently been strongly associated with AS susceptibility in Korean and Han Chinese patient cohorts.[19,27]

The delineation of a shared genetic architecture has been further advanced by Ellinghaus et al.[28] Utilising high-density immuno-chip genotyping data from five spondyloarthritis spectrum and associated diseases (AS, CD, ulcerative colitis [UC], psoriasis, and primary sclerosing cholangitis), this study identified a total of 187 non-MHC risk loci, which were shared between two or more of these diseases.[28] Among the strongest shared AS/CD loci were the intronic SNP rs2910686 in *ERAP2*, the missense SNP rs12720356 in *TYK2*, and the intronic variant rs679574 in *FUT2* (Table 1). These associations again point to the importance of the gut microbiome and mucosal immunity in both AS and CD. Endoplasmic reticulum aminopeptidases 2 (ERAP2), along with ERAP1, are key players in the adaptive immune response of the gut and the joint.[29] These enzymes trim peptides arising from infection or cell damage. The ERAP1- and ERAP2-trimmed peptides are then loaded onto MHC-1 molecules and displayed on the surface of affected cells, triggering a T-cell-mediated immune response against these cells in the gut mucosa or joint.[29] Pepelyayeva et al.,[30] using an *ERAP1* knockout mouse model, demonstrated that ERAP proteins play a central role in both preventing inflammation and in maintaining homeostasis of gut microbiota. ERAP1-deficient mice were significantly more likely to develop severe colitis after dextran sulphate sodium challenge compared to wild-type mice. Furthermore, this knockout model exhibited marked gut dysbiosis and developed many of the hallmarks of axial SpA including sacroiliitis, joint erosions, and spinal ankylosis.[29,30] Tyrosine kinase 2 (TYK2) is an intracellular signalling protein, which belongs to the JAK family.[31] This protein plays a pivotal role in the expansion and maturation of Th17 cells through the activation of IL23R–STAT3 signalling.[31] Murine models of colitis and SpA have demonstrated the specific inhibition of TYK2 ameliorates both intestinal and joint inflammation.[31] Fucosyltransferase 2 (FUT2) is responsible for the synthesis of the H antigen on the intestinal mucosa; this H antigen is an oligosaccharide moiety that acts as both an attachment site and carbon source for the intestinal microbiome.[32] Individuals who are homozygous for loss-of-function alleles of *FUT2* exhibit significant intestinal dysbiosis and have increased susceptibility to CD.[32]

Collectively, the findings of these genetic studies suggest CD and AS do indeed have significant shared genetic architecture (Table 1), and that shared clinical characteristics relate to shared pathophysiological pathways. These studies also highlight the possibility that concomitant disease may represent a genetically distinct population.

GENE MICROBIAL INTERACTIONS IN ANIMAL MODELS AND HUMANS

Several, not necessarily mutually exclusive, theories have been proposed to explain the overlap between AS and CD, including the gut–joint axis of inflammation (Figure 1).[33] Central to this hypothesis is the concept that mucosal immunity and the perturbations in the intestinal microbiome in genetically susceptible individuals may instigate and perpetuate both gut and joint inflammation.[33]

The first evidence to support this hypothesis came from studies in HLA-B27 transgenic rats.[34] These rats developed a spondylitis-like syndrome under normal conditions; however, when raised in a germ-free environment, colitis, arthritis, and skin disease associated with this animal model dramatically improved.[34] Certain bacterial strains, when introduced to these germ-free rats, were found to maintain remission while other bacterial strains caused relapse.[35] A more recent SpA–CD animal model, the SKG mouse, provided further evidence of the role of host genetics and microbes in the development of SpA and IBD. This model is a BALB/c mouse strain that carries the SKG ZAP-70 *W163C* mutation.

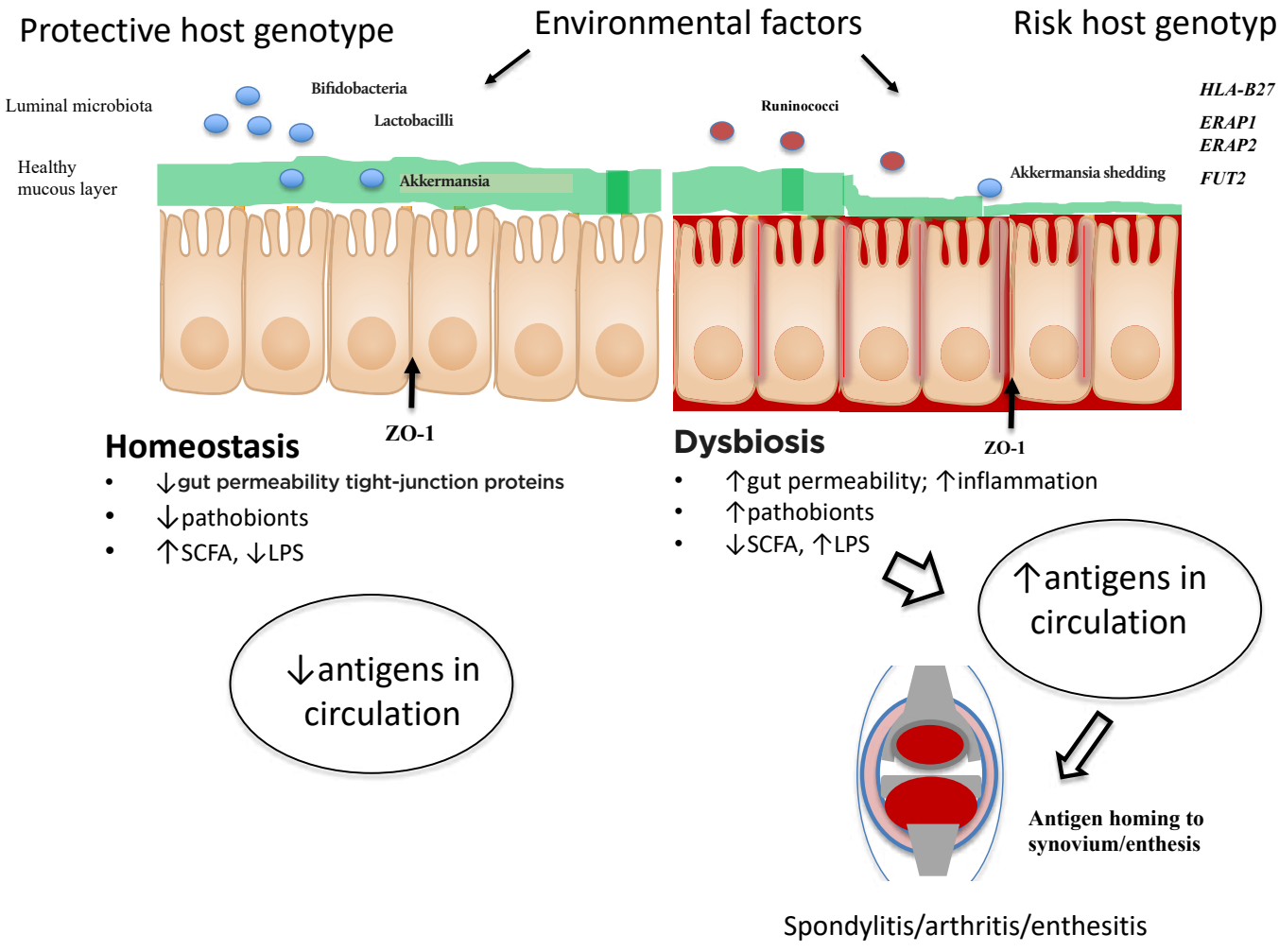

Figure 1: A proposed schema for the role of gut microbiota and host genetics in gut and joint inflammation.

Gut inflammation and increased epithelial permeability result in dysbiosis, mucin layer degradation, and tight-junction protein abnormalities (e.g., ZO-1). Transposition of luminal antigens into the lamina propria stimulates pro-inflammatory pathways and antigens are presented by dendritic cells through HLA Class I proteins. High antigenic loads lead to translocation of these antigens to the joint, resulting in aberrant inflammation.

HLA: human leukocyte antigen; LPS: lipopolysaccharide; SCFA: short chain fatty acids; ZO-1: zonula occludens 1.

Under germ-free conditions, SKG mice remain healthy; however, when exposed to curdlan, an antigen derived from the cell walls of yeast, fungi, and bacteria, the *W163C* mutation causes SKG mice to develop a SpA-like disease with arthritis and small intestinal inflammation.[36] The SKG mouse model was developed to study auto-reactive CD4+ T cells via an IL-23-dependent pathway known to be pivotal in the pathogenesis of both IBD and SpA.[37]

Observations made in ReA provide further evidence to support a central role for host genetics and microbes in both SpA and IBD, and the existence of the gut–joint axis of inflammation. ReA, part of the SpA spectrum, can be triggered by an enteric infection with a number of organisms including *Salmonella* and *Shigella*.[38] Individuals who are HLA-B27-positive are more than five times more likely to develop an arthritis after exposure to a triggering organism than those who do not carry this allele.[39] The exact mechanism for this is still speculative, but *Salmonella* antigens have been shown to be immunogenic to mononuclear cells within joint synovial fluid.[40]

INTESTINAL MICROBIOTA AND ITS ROLE IN DISEASE IN PATIENTS WITH SPONDYLOARTHROPATHIES

The human intestine contains a unique microbiota, which maintains a relatively stable ecological state with a dynamic equilibrium. An individuals' microbiota is highly resistant to change, with key species maintained over long periods. However, microbial profile and abundances do change over a persons' lifetime, with diet and other exogenous factors influencing its composition. The overall resilience of the resident flora can be impacted by major perturbations, which can lead to a 'tipping point' beyond which homeostasis fails and significant shifts in microbial profiles can occur.[41] The colonising microbiota is largely acquired at birth, although some elements may even be acquired *in utero*.[42] Mode of delivery, whether vaginal or via Caesarean section, can influence early acquisition of the microbiota.[43] This microbiota is essential to the development of the intestinal immune system, which in turn influences the constituents of the microbiota.[44] A recent comprehensive study of the human gut microbiota identified 204,938 non-redundant genomes from 4,644 gut microbes, many of which are specific to individual human populations.[45] Moreover, metabolomics studies have demonstrated that the small-molecule metabolites produced by the microbiota can profoundly alter host–gut microbiota interactions and thereby intestinal inflammation, and potentially joint inflammation (Figure 1).[44]

Transient or permanent perturbations, or dysbiosis, of the gut microbiota have been associated with CD, UC, and irritable bowel syndrome. Attempts have been made to quantify these perturbations, such as the GA-map™ Dysbiosis Index (Biohit Healthcare Ltd, Helsinki, Finland), which uses faecal samples from patients and compares the result with population norms,[46] although such approaches have been criticised for not recognising the dynamic nature of the gut microbiota.[47]

An important, unresolved question is whether the gut microbiota is a causative factor for gut inflammation in SpA or whether changes in the microbiota are a product of inflammation. Animal models seem to suggest a causative role for the interplay of gut microbiota with host genetics. However, host genetics appear to play only a minor role in determining the composition of the microbiota, as shown by twin studies, accounting for no more than 8% of microbiota variability. Furthermore, unrelated individuals in the same household share common constituents, with approximately 20% of the variability in the microbiome between individuals resulting from diet, drug therapies, and body habitus.[48] These findings raise the question of whether it is possible to manipulate the gut microbiota before the development of clinical disease.

Several studies have investigated the gut microbiota in SpA. One study looked at the dysbiosis of faecal microbiota in 150 patients with AS, 18 patients with UC, and 17 healthy controls.[49] Dysbiosis was defined as a Dysbiosis Index of ≥3. Using this definition, 87% of patients with AS had dysbiosis.[49]

A recent study used shotgun meta-genomic sequencing and metabolomics to analyse faecal microbiota in a case-control cohort of 250 subjects.[50] Cases and controls had different microbiota profiles, with a prevalence in AS

patients of bacterial species thought to be pro-inflammatory.[50] Furthermore, the gut microbiota of patients with AS carried a higher load of bacterial peptides known to be presented by HLA-B27, suggesting either HLA-B27 fails to clear these or that these peptides drive the immune response associated with HLA-B27.[50]

POTENTIAL NEW THERAPEUTIC TARGETS AND APPROACHES

Whilst most studies still focus on quantity and diversity of the microbiota, investigating the metabolic effects, or metabolomics, of the gut microbiota is increasingly recognised as having greater potential for developing new therapies.

Mucin Barrier

An example of this more targeted approach to microbiota analysis is illustrated by studies of the mucin barrier in the gut. In the healthy gut, bacteria predominantly reside in the gut lumen, with few able to penetrate into the mucus layer. Mucin 2 (Muc2) is the main constituent of the mucus layer, the integrity of which is maintained by glycosylation reactions within the intestinal epithelial cells, which are stimulated by IL-22. This process seems to be key in maintaining the equilibrium between host and gut bacteria (Figure 1). The microbiota induces expression of host fucosyltransferase 2 and a deficiency of fucosyltransferase 2 has been noted to cause migration of leucocytes into the caecum epithelium following infection with *S. typhimurium*.[51]

The importance of an intact mucus layer for gut microbial tolerance is demonstrated by numerous studies. Attenuation of the mucin barrier is a stimulus for intestinal inflammation. A thin mucus layer is associated with increased bacterial invasion in IBD. Mouse models deficient in Muc2 induce the Th17 cells and Th1 responses, and reduced Muc2 levels are detectable in patients with UC prior to the onset of inflammation.[51]

The mucin-degrading commensal *Akkermansia muciniphila* is of particular interest. This bacterium resides in the mucus layer and can restore mucus thickness and the mucin barrier; it is also thought to contribute to improving the symbiosis between host and microbiota.[52]

A reduction in the abundance of *A. muciniphila* and a corresponding increase in Ruminococcus species is seen in CD. *R. gnavus* produces an inflammatory polysaccharide, produced in abundance during flares of CD.[53] An increase in Ruminococcus species is also seen in SpA.[54]

Fucose, a natural monosaccharide, has been shown to ameliorate colitis in an experimental animal model by improving dysbiosis, including a reduction of Ruminococcus species.[55] There is also interest in using *A. muciniphila* as a probiotic species (see later).

Short Chain Fatty Acids

Dietary fibres are metabolised by colonic bacteria to short chain fatty acids (SCFA), such as lactate. These metabolites are essential for maintaining immune tolerance and promoting symbiosis between the host and the gut microbiota. SCFAs inhibit intestinal inflammation by mediating the host immune response and may also prevent pathogen colonisation.[51] Reduced levels of SCFA have been found in the faecal samples of patients with IBD.[56] Furthermore, in the HLA-B27 transgenic rat model the intestinal metabolome differs from wild-type rats within weeks of birth. In this model SCFAs attenuate inflammatory disease.[57]

Lipopolysaccharides

Lipopolysaccharide (LPS) is expressed on the outer surface of Gram-negative bacteria and is a crucial signalling molecule recognised by immune cells and binds to CD14 and TLR4 receptors on these cells. Modification of LPS enables pathogens to evade the immune system. LPS also directly induces intestinal inflammation, disrupting intestinal tight junctions and increasing gut permeability. Dysbiosis has been shown to increase the prevalence of pathobionts and LPS in patients with IBD.[51] In AS, the increase in gut permeability is associated with the translocation of LPS and other bacterial products across the mucosa, with LPS stimulating IL-23 production.[58]

APPROACHES TO THE CLINICAL ASSESSMENT AND MANAGEMENT OF BOWEL INFLAMMATION IN PATIENTS WITH SPONDYLOARTHROPATHIES

There is increasing evidence to suggest that patients with SpA and concomitant bowel inflammation may be a genetically and microbiome-distinct patient subgroup.[33] This subgroup presents a number of significant clinical challenges. Identifying patients with AS/SpA who have bowel inflammation is challenging.[5] Recommendations to improve identification of patients with coexisting IBD/SpA include education of primary care physicians and developing shared clinics with gastroenterologists.[11] Some centres have trialled clinical pathways in an attempt to more readily identify these patients.[59] A combination of patient questionnaires (such as the Dudley Inflammatory Symptoms Questionnaire [DISQ]), faecal calprotectin, and CRP may help to identify patients who should go forward for more invasive studies such as colonoscopy or capsule endoscopy.[5,59] A further opportunity to identify patients with sacroiliitis is afforded by the routine assessment of the sacroiliac joints in patients with IBD who undergo MR enterography to evaluate the extent and complications of their IBD. Small studies have shown this is feasible and an effective way of identifying patients with sacroiliitis and further studies are planned.[60]

Concomitant IBD and SpA has implications for management using existing standard therapies. Non-steroidal anti-inflammatory drugs may worsen bowel inflammation. Similarly, the TNF receptor blocker etanercept and the IL-17 monoclonal antibody secukinumab, which are effective for treating moderate to severe AS, do not ameliorate, and in the latter case may actually worsen, bowel inflammation. To date, the established monoclonal antibody therapies such as adalimumab and infliximab are the best therapies for IBD/SpA overlap.[61] More recently, evidence for favourable outcomes in both AS and IBD has also been seen in studies of JAK inhibitors such as tofacitinib.[62]

MICROBIOTA RESEARCH REVEALS POTENTIAL FUTURE THERAPIES

At present, the state of knowledge is insufficient to recommend specific treatment modalities in AS/SpA. However, existing therapies have been shown to affect the microbiota and several areas of research show promise for future therapies.

Prebiotics

Prebiotics are substrates not digested in the human small bowel but available to the microbiota. Supplementary dietary fibre and anaerobic fermentation produces SCFA, which may promote a selective pressure towards a beneficial colonic microbiota. Prebiotics have shown benefit in several animal models of gut inflammation.[56] No studies are available in AS, but several small studies have been undertaken in IBD. In one of these, a double-blind pilot study in patients with active UC, using oral inulin, an oligofructose supplement, a decrease in symptoms and reduced faecal calprotectin levels were noted.[56]

Exclusive Enteral Nutrition

Exclusive enteral nutrition (EEN) has been used widely in paediatric CD. It has shown particular promise in recent-onset CD, resulting in higher remission rates and a trend towards better growth, although relapses and complication rates were similar to patient cohorts receiving conventional therapy.[64] However, a Cochrane review of adults with established quiescent CD could make no firm conclusions regarding the efficacy or safety of EEN.[1]

A more recent study of diet intervention, which replicated elements of EEN, showed changes in the microbiota and a decrease in gut inflammation in patients with active CD.[65] To date, there have been no studies of EEN in SpA.

Probiotics

A single, small, randomised trial in AxSpA of an oral probiotic containing Bifidobacteria, a lactobacillus, and *Streptococcus salivarius* found no significant benefit in primary outcomes.[66] However, since this study more promising probiotic candidates, specifically *A. muciniphila* have emerged. Currently studies exploring *A. muciniphila* as a therapeutic candidate have only been performed in animal models, but future studies in human IBD and SpA are likely.[52]

Faecal Microbiota Transplant

Faecal microbiota transplant involves the transfer of pre-screened minimally manipulated stool from healthy donors into the gastrointestinal tract of a recipient, via enema or nasogastric

tube, with the purpose ameliorating dysbiosis. The place of faecal microbiota transplant in the management of colitis due to *Clostridium difficile* is well established and guidelines have been developed internationally for its use in this situation.[67] Several small studies have shown promise in ameliorating colitis in UC, but as yet this has not been translated to therapy beyond clinical trials.[68] A small study is underway in patients with psoriatic arthritis.[69]

CLINICAL AND RESEARCH CONSEQUENCES OF THE INTERPLAY OF GUT MICROBIOTA AND HOST GENETICS

Research priorities for the future should build on the expanding knowledge of the gut microbiota and gut inflammation. Improved risk stratification of close relatives of index cases, through polygenic risk scores, could identify individuals at high risk. Early assessment and microbial analysis may then identify individuals with modifiable dysbiosis. These individuals may be ideal candidates for novel microbial therapies designed to protect and enhance the mucin layer and select out pro-inflammatory microbiota. There is much work to be done in human populations to delineate the interplay between host genetics and the microbiota, but preliminary results show definite promise for an effective preventive approach in the future.

KEY LEARNING POINTS

- Significant phenotypic overlap exists between SpA and CD.
- Patients with SpA and concurrent CD present clinical management challenges.
- There is increasing evidence to suggest that the interplay between host genetics and gut microbiota is central to this overlap.
- Understanding this interplay may provide novel therapies for improved management of concurrent SpA and CD.

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Performance of Different Criteria Sets for Inflammatory Back Pain in Radiographic and Nonradiographic Axial Spondyloarthritis

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Abstract

Introduction: It is important to recognise inflammatory back pain (IBP) for early diagnosis of ankylosing spondylitis (AS). The aims of this study were to develop a valid, reliable Bengali IBP tool and to assess the performance of different IBP criteria sets, including Calin, Berlin set 8a and 7b, and new Assessment of SpondyloArthritis International Society (ASAS) expert criteria, in radiographic axial spondyloarthritis (axSpA) and nonradiographic axSpA.

Method: This case-control study was performed in three phases. The first phase involved development of an IBP tool by adding the fifth parameter of ASAS expert criteria to the National Health and Nutrition Examination Survey (NHANES) 2009–2010 arthritis questionnaires; the second phase assessed reliability by test-retest statistics among 87 participants at a 5-day interval. Finally, according to the imaging arm of ASAS axSpA classification criteria, 50 patients with axSpA were included as cases while 50 patients with chronic mechanical back pain (MBP) were included as a control.

Results: The presence of IBP with SpA versus patients with MBP, detected by Calin criteria, were 76.0% versus 10.0%, by Berlin 8a were 72.0% versus 6.0%, by Berlin 7b were 58.0% versus 12.0%, and by ASAS were 64.0% versus 18.0%, respectively. Results suggested the Calin criteria set has the highest sensitivity (76.0%) and Berlin set 8a has the highest specificity (78.9%) in the differentiation of IBP from MBP.

Conclusion: The performance of the new ASAS criteria was analogous to the other existing criteria sets. The highest positive likelihood ratio and odds ratio were found for Berlin set 8a criteria.

The Berlin set 8a criteria can still be used in primary care practice at the first screening because of high sensitivity.

INTRODUCTION

Back pain is a very common problem worldwide. It is the most frequent reason for visits to the physician.[1-5] Approximately 80% of the world's population develops low back pain at some point in their adult life. Back pain is considered chronic when it persists for 3 months or more. This chronic condition may reflect inflammatory back pain (IBP) or mechanical back pain (MBP). Approximately 38.7% of patients with chronic back pain have IBP.[6] This IBP is the earliest symptom of axial and other forms of spondyloarthritis (SpA).[7-11] The sacroiliac joint is the primary site of inflammation.[12] The presence of sacroiliitis in the pelvic X-ray, according to modified New York criteria, defines radiographic SpA; the presence of bone marrow oedema, synovitis and capsulitis, enthesitis, subchondral sclerosis, erosions (marginal foci or articular bone loss), periarticular fat deposition, and ankylosis in the MRI short TI inversion recovery image defines nonradiographic axial spondyloarthritis (axSpA). Axial spondyloarthropathy includes classical ankylosing spondylitis (AS) as well as axSpA. Inflammatory changes in the entire axial skeleton are characteristic of axSpA and can be visualised by MRI; structural alterations, such as new bone formation with syndesmophytes and ankylosis, develop later in the course of the disease. AS is defined by the presence of sacroiliitis on X-ray and other structural changes on spine X-rays, which may eventually progress to bony fusion of the spine.[4] Males tend to be more commonly affected than females.[12] AS primarily affects young adults, with a higher incidence in patients <45 years old.

Clinical features of axial SpA or AS include IBP, alternating buttock pain, enthesitis, arthritis, dactylitis, acute anterior uveitis, a positive family history, and a good response to nonsteroidal anti-inflammatory drugs. Among these features, IBP is often present at disease onset.[13] Over recent decades, it has become increasingly evident that in many patients with AS or SpA, it takes many years to develop radiographic sacroiliitis from the onset of IBP.[14] The higher prevalence rate of SpA in this subcontinent has become a prime concern.[15] As IBP is the key clinical symptom, it is very important to recognise IBP for early diagnosis of axSpA or AS.[16] To detect IBP, powerful tools or tests are needed, not only for the diagnosis of patients with AS,[12,17] but also for the diagnostic evaluation of patients with chronic back pain.[18,19]

Up to now, several criteria sets have been developed that measure IBP. In chronological order, these criteria sets include Calin,[16] modified New York criteria for ankylosing spondylitis,[20] Amor,[21] European Spondyloarthropathy Study Group (ESSG),[22] Berlin,[23] and Assessment of SpondyloArthritis International Society (ASAS) criteria.[23,24] Although these criteria sets share many common clinical features, they diverge on some parameters such as age limit, mode of onset of pain, duration of pain, presence of morning stiffness or night pain, and improvement of pain with rest or exercise, which may be responsible for the difference between their reported sensitivity and specificity. The Berlin criteria have two subsets, Berlin set 8a and 7b, which differ in the number and variation of their parameters. However, there are no published data in Bangladesh, as well as in this subcontinent, regarding the performance of these IBP criteria sets.

AIMS

To develop a valid, reliable Bengali IBP tool and to assess the performance of Calin, Berlin, and the new ASAS expert criteria in patients with axSpA and nonradiographic axSpA by using a control group of patients with chronic MBP for ≥3 months. This study also aims to help determine which criteria sets are better to recognise the presence IBP in the Bengali population.

MATERIALS AND METHODS

Following the minimum prevalence rate of IBP in the previous studies, the authors recruited participants >20 years of age from the outpatient department of the Medicine department of Chattogram Medical College. A convenience

method of sampling was followed. Medical data were collected from patients who were either consulted spontaneously or referred for further evaluation by Medicine Indoor or Physical Medicine Indoor of Chattogram Medical College Hospital, from April 2019 to September 2019.

The study was performed in three phases. In the first phase, translation of the English National Health and Nutrition Examination Survey (NHANES) 2009–2010 Arthritis Questionnaire (ARQ) into Bengali was completed, according to Beaton et al.[25] translation procedure (ARQ010, ARQ020, ARQ024, ARQ025, ARQ022, ARQ040, ARQ060, ARQ073, ARQ077, ARQ080, and ARQ100 were translated). The intraclass coefficient was 0.8, with a 95% confidence interval (CI) having a width of 0.1, so a minimum of 37 subjects were required to assess reliability statistics of any instrument. In this study, for test-retest reliability, the translated version of the Bengali IBP tool was administered among 50 participants; out of 50 participants, only 37 subjects participated in a retest by the same assessor at a 5-day interval. In the third phase, the performance of different IBP criteria sets was assessed by the Bengali IBP tool, where the sample size was 100 participants who attended the outpatient and inpatient departments of the Medicine and Physical Medicine department with chronic back pain for ≥3 months. Fifty patients with axSpA, diagnosed according to the imaging arm of ASAS axSpA classification, who had chronic back pain for ≥3 months with radiographic sacroiliitis by modified NY criteria or sacroiliitis on MRI short TI inversion recovery image, were included as study cases. The control group of 50 patients were those with a diagnosis of chronic (≥3 months) MBP, with a normal pelvic radiograph as well as normal MRI of sacroiliac joints. Because ankylosing spondylitis is not the only cause of IBP, exclusion of other diseases was confirmed by MRI of the whole spine when necessary.

Statistical Analysis

Sensitivity and specificity were measured by 2x2 contingency table. According to the empirical nonparametric method, receiver operating characteristic analyses were performed to evaluate the performances of the Bengali version of Calin, Berlin set 8a, Berlin set 7b, and ASAS IBP criteria, and the area under curve (AUC) were computed for each criterion. Receiver operating characteristic curves provided a graphical representation of the overall accuracy of a test by plotting sensitivity against specificity for all thresholds, while the AUC quantified the accuracy of the test. This study also calculated positive and negative likelihood ratio (+LR, -LR), positive predictive value (PPV), and negative predictive value (NPV) to evaluate the external validity of each tool. The ability of the tools to detect IBP was also evaluated in patients with SpA. Statistical analysis used SPSS® (Version 23.0; IBM, Endicott, New York, USA).

RESULTS

Firstly, the different IBP criteria sets are defined (Table 1),[16,23,24] with results explained successively.

Table 1: Criteria sets for inflammatory back pain.

Calin et al.,[16] 1977	Berlin[23] set 8a	Berlin[23] set 7b	ASAS[23,24]
1. Age at onset <40 years 2. Back pain >3 months 3. Insidious onset 4. Associated with morning stiffness 5. Improves with exercise	1. Morning stiffness >30 min 2. Improves with exercise but not with rest 3. Awakening at second half of the night because of back pain 4. Alternating buttock pain	1. Morning stiffness >30 min 2. Improves with exercise but not with rest 3. Age at onset <30 years	1. Age at onset <40 years 2. Insidious onset 3. Improves with exercise 4. No improvement with rest 5. Pain at night (improves upon getting up)
If ≥4 out of 5 parameters are present	If ≥2 out of 4 parameters are present	If ≥2 out of 3 parameters are present	If ≥4 out of 5 parameters are present

A total of 100 respondents were enrolled in this study. The mean age of the SpA group was 39.30 (±13.31) years, and 35.58 (±14.56) years in the MBP group. In both groups, 54.0% of participants were male, and 46.0% were female. Most of the patients in the SpA group were aged 40–49 years (38.0%), and 19–29 years (39.6%) in the MBP group. Most of the patients belonged to urban areas: approximately 27 in the SpA (61.4%) and 34 in the MBP (75.6%) groups. Among patients with SpA, 34.7% (n=17) had completed their primary level education, whereas 31.3% (n=15) of patients had completed the graduation level of their education. In both groups, employment role of homemaker was predominant: approximately 19 (43.2%) of the SpA and 11 (25.6%) of the MBP group. Among the clinical characteristics of both groups, the duration of disease in the SpA group was 115 (±79) months and 62 (±7) months in the MBP group. Biochemically, the level of haemoglobin was near to equal in both groups. The levels of C-reactive protein (CRP) were significantly higher in the SpA group (25.95±30.24) than patients with MBP (2.41±1.09) because it is a clinical feature of SpA. Serum glutamic pyruvic transaminase levels were relatively higher in patients with SpA (55.83±76.38) compared with the MBP group (0.81±0.12). Among the features of SpA, in the case group elevated CRP levels were predominant in 39 (79.6%) patients. Other features were good response to nonsteroidal anti-inflammatory drugs in 36 (73.5%), arthritis in 25 (51.0%), and enthesitis in 18 (36.0%) patients in this group. A history of anterior uveitis was present in 4 (8.3%) cases; a positive family history of SpA was found in only 4 (8.3%) patients and psoriasis in 3 (6.0%) patients in the case group. The SpA features were absent in the MBP group as exclusion criteria. In the imaging, most patients presented with bilateral sacroiliitis (76.0%; n=38), and unilateral sacroiliitis was found in 24.0% (n=12) of cases. The calculated Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for 50 patients with axSpA was 2.780 (±1.232).

Among the available criteria sets for the definition of IBP, the Calin criteria had the highest sensitivity (76%), while the Berlin set 8a criteria had the highest specificity (94%). The Berlin set 8a also had a sensitivity (72.0%) near to Calin. The recently described ASAS IBP criteria showed the most balanced performance, with no clear superiority over the other two criteria sets (sensitivity: 64%; specificity: 82%). The highest +LR was 12 (95% CI: 3.952–36.436) for Berlin set 8a criteria. A comparison of different IBP criteria sets is shown in Table 2.[16,23,24]

The individual performance of IBP items revealed some significant findings. IBP item 'pain improves with activity, not with rest' showed the highest sensitivity (97.0%); the best specificity was found for 'morning stiffness >30min' (88.0%). The highest +LR of 9.50 (95% CI: 9.49–9.50) was observed for the item 'pain awakens second half of night'. 'Pain response to exercise' showed a significant odds ratio (OR) of 8.367 (95% CI: 3.610–19.395). The performance of individual items of the criteria sets for the detection of IBP is shown in Table 3.

DISCUSSION

With a few exceptions in demographic features, the clinical features and results of previous studies were similar to that of the present study. 50% of study subjects in both the SpA and MBP groups had an education qualification above secondary school. The study included 43% homemakers and 34% service holders with SpA; on the other hand, the MBP group comprised 30% students and 26% homemakers.

Among the clinical variables, all patients with SpA had higher CRP values (25.95±30.24) compared with controls (2.41±1.09). The presence of IBP among the patients with SpA and MBP, detected by Calin, Berlin set 8a, Berlin set 7b, and ASAS criteria, were 76.0% and 10.0%, 72.0% and 6.0%, 58.0% and 12.0%, and 64.0% and 18.0%, respectively. The estimated BASDAI for patients with axSpA was 2.780 (±1.232). Assessment of individual performance of IBP items revealed some significant findings. The item 'age at onset' showed good sensitivity (78.0%) and low specificity (16.0%) for SpA, which was consistent with other studies.[26] The item 'insidious onset' was not clarified by previous studies or by the original developers of various criteria sets. As per the structure of the NHANES questionnaire, there were various options for the item 'insidious onset'. It was measured in terms of two options in this study: 'over 3 weeks' and 'month up to a year'.

Table 2: Statistical validation of criteria with diagnostic test.

	Gold-standard test		Estimate (95% CI)
	IBP (-ve)	IBP (+ve)	
Calin et al.,[16] 1977			
Case	12 (21.1%)	38 (88.4%)	Sensitivity: 0.760 (0.626–0.857)
Control	45 (78.9%)	5 (11.6%)	Specificity: 0.900 (0.786–0.957)
Total	57 (100.0%)	43 (100.0%)	PPV: 0.884 (0.755–0.949)
Significance	0.000		NPV: 0.789 (0.667–0.875)
			+LR: 7.600 (3.261–17.710)
			-LR: 0.267 (0.161–0.440)
Berlin[23] set 8a			
Case	14 (23.0%)	36 (92.3%)	Sensitivity: 0.720 (0.583–0.825)
Control	47 (77.0%)	3 (7.7%)	Specificity: 0.940 (0.838–0.979)
Total	61 (100.0%)	39 (100.0%)	PPV: 0.923 (0.797–0.973)
Significance	0.000		NPV: 0.770 (0.651–0.858)
			+LR: 12.000 (3.952–36.436)
			-LR: 0.298 (0.190–0.467)
Berlin[23] set 7b			
Case	21 (32.3%)	29 (82.9%)	Sensitivity: 0.580 (0.442–0.706)
Control	44 (67.7%)	6 (17.1%)	Specificity: 0.880 (0.762–0.944)
Total	61 (100.0%)	39 (100.0%)	PPV: 0.829 (0.673–0.919)
Significance	0.000		NPV: 0.677 (0.556–0.778)
			+LR: 4.833 (2.201–10.616)
			-LR: 0.477 (0.339–0.672)
ASAS[23,24]			
Case	18 (30.5%)	32 (78.0%)	Sensitivity: 0.640 (0.501–0.759)
Control	41 (69.5%)	9 (22.0%)	Specificity: 0.820 (0.692–0.902)
Total	61 (100.0%)	39 (100.0%)	PPV: 0.780 (0.633–0.880)
Significance	0		NPV: 0.695 (0.569–0.797)
			+LR: 3.556 (1.899–6.656)
			-LR: 0.439 (0.297–0.650)

CI: confidence interval; IBP: inflammatory back pain; LR: likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; -ve: negative; +ve: positive.

Table 3: Individual performance of inflammatory back pain items.

Items	Sensitivity	Specificity	+LR (95% CI)	-LR (95% CI)	p value	OR (95% CI)
Insidious onset	65.8	57.4	1.56 (1.55–1.57)	0.59 (0.59–0.59)	0	1.08 (0.740–1.580)
Age at onset back pain <30 years	44	40	1.37 (1.36–1.38)	1.4 (1.40–1.40)	0	0.73 (0.490–1.080)
Age at onset back pain <40 years	78	16	1.08 (1.08–1.08)	1.37 (1.37–1.37)	0	0.929 (0.767–1.125)
Morning stiffness >30 min	54	88	4.5 (4.49–4.50)	1.92 (1.92–1.92)	0	4.5 (2.036–9.945)
Pain improves with exercise or activity	85	81	8.36 (8.36–8.36)	5.55 (5.55–5.55)	0	8.367 (3.610–19.395)
Pain improves with activity, not with rest	97	15	8.2 (8.19–8.20)	5 (5.00–5.00)	0	1.25 (1.088–1.436)
Pain awakens second half of night	59	70	9.5 (9.49–9.50)	1.56 (1.56–1.56)	0	1.973 (1.117–3.198)
Alternating buttock pain	84	70	2.8 (2.50–2.91)	0.29 (0.28–0.30)	0	2.8 (1.803–4.349)
Pain at night (improves with getting up)	76	34	1.15 (1.15–1.15)	0.7 (0.70–0.70)	0	1.152 (0.894–1.483)

CI: confidence interval; LR: likelihood ratio; OR: odds ratio.

The sensitivity and specificity were 98.0% and 14.0%, respectively, for the option 'over 3 weeks', which is a very poor trade-off with specificity in the case of SpA and dissimilar to other studies. However, the sensitivity and specificity became 65.8% and 57.6% for the option 'month up to a year', and the OR also became 1.080. The present study was structured with the NHANES questionnaire, which had only one option: 'morning stiffness >30 minute'. The study showed 70.0% sensitivity and 58.0% specificity, with a significant OR of 4.50 (95% CI: 2.036–9.945).

'No improvement with rest' achieved 90.0% sensitivity and 15.0% specificity. The item 'improves with exercise but not with rest' instead of item 'no improvement with rest' had higher specificity (90.0%), along with a significant OR of 1.250 (95% CI: 1.088–1.436). Regarding 'awakening during the second half of the night', the scoring reflected the consolidated positive response for one of two options: 'wake up after have been sleeping for 4 or more hours' and 'kept from sleeping for more than 4 hours at a time'. Sensitivity (59.0%) and specificity (70.0%) of the item that indicated 'nocturnal pain' was also consistent.

The last IBP item, 'alternating buttock pain', showed a significant difference between this study (84.0% sensitivity and 70.0% specificity) and past studies. Besides this, when components of IBP criteria sets were analysed individually, the highest OR were observed for 'pain improves with exercise but not with rest', 'pain improves with exercise or activity', and for 'morning stiffness'. The highest +LR of 9.5 (95% CI: 9.49–9.50) and OR of 8.367 (95% CI: 3.610–19.395) were observed for 'pain awakens second half of night' and 'pain improves with exercise or activity'. Therefore,

considering the duration of morning stiffness >30min, Calin's sensitivity (88.4%) and specificity (78.9%) were consistent with the sensitivity and specificity of the other previous study.[27]

Regarding AUC assessment, Calin cover 0.830 (95% CI: 0.749–0.911) area, which also indicates the validity of this study. +LR of 7.6 (95% CI: 3.261–17.71) and disease prevalence of 0.50 (95% CI: 0.398–0.602) were found for Calin in this study.

In this study, the sensitivity and specificity of the Berlin set 8a criteria were 72.0% and 94.0%, respectively. The specificity (82.0%) of this study was consistent with the ASAS validation study (91.4%).[27] Amongst individual items of IBP, the highest sensitivity (84.0%) for SpA was that of 'alternating buttock pain'. Berlin set 7b and 8a criteria have similar item combinations, except that 'alternate buttock pain' is not an item of Berlin set 7b. With this reduced item set, the sensitivity of Berlin set 7b came to be lower than set 8a, but was consistent (58.0%) with the previous studies;[26,27] the sensitivity of 'alternating buttock pain' might be responsible for this difference.

Regarding AUC analysis, it was found that Berlin set 8a covered >0.830 (95% CI: 0.745–0.915) area, had +LR of 12 (95% CI: 3.952–36.436), and had a prevalence of 0.50 (95% CI: 0.3983–0.6017). AUC curve analysis showed that ASAS criteria covered 0.730 (95% CI: 0.629–0.831) area; a +LR of 3.556 (95% CI: 1.899–6.656) and prevalence of 0.50 (95% CI: 0.3983–0.6017) were found.

CONCLUSION

In conclusion, this study was to develop a valid, reliable Bengali IBP tool to assess the prevalence of IBP among the 260 million Bengali population living around the world. These tools also help the physician to assess IBP among the Bengali people. Moreover, performances of all IBP criteria sets are not the same around the world. These results suggest that among the available criteria sets for the definition of IBP, the Berlin set 8a criteria had a sensitivity of 72% and the highest specificity (94%). Berlin set 8a also showed the specificity nearest to Calin. The recently described ASAS IBP criteria showed a balanced performance, with no clear superiority over the other two criteria sets.

The highest +LR was found for Berlin set 8a criteria. The Berlin 8a criteria set can be advocated for use in primary care practice because sensitivity is important at the first screening, while specificity becomes more important at higher levels of care.

Limitations

- Due to financial constraints and time limitations, this study was conducted in a small population. With future financial support, this study can be conducted in a large population.
- This is a screening test. This study included cases and controls according to the imaging arm of ASAS axSpA classification criteria, which is already established.
- There may be a chance of some degree of recall bias.

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