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EMJ Rheumatology

Review of EULAR 2023

Editor's Pick

Evaluation of Xerostomia in Sjögren's Syndrome and Its Impact on Quality of Life and Nutritional Status: A Cross-Sectional Study

Interviews

Chris Wincup, Denis Poddubnyy, Christine Peoples, and Thomas Huizinga share insights from their career and research

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Aims and Scope

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Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Dear Readers,

Welcome to this issue of *EMJ Rheumatology*. In this issue, we bring you the latest from the European Alliance of Associations for Rheumatology (EULAR) 2023 Congress, which took place in Milan, Italy, at the end of May as a live event. This year, the congress focused on live interactions and networking, aiming to provide the essence of the 'congress experience'. Particular highlights this year were presentations on diagnosis of rare rheumatic diseases and the treat-to-target concept, discussing how this theory is best put into practice.

It is with great pride that we feature exclusive interviews with experts in rheumatology Chris Wincup, Denis Poddubnyy, Christine Peoples, and Thomas Huizinga, who discussed topics such as systemic lupus erythematosus (SLE), spondyloarthritis, and the value of telemedicine, among others.

Those of you who are interested in SLE in particular will enjoy our infographic on SLE, focusing on the ambiguity in diagnosis of this condition. This infographic is a great tool in highlighting steps that can be taken to improve diagnosis of SLE and recommendations for the future.

Xerostomia is a symptom that affects people with Sjögren's syndrome and the cross-sectional study on xerostomia featured in this issue explores the impact of this symptom on quality of life and nutritional status in this patient group. The study highlights the importance of including nutritional status and advice in the evaluation of patients with primary Sjögren's syndrome.

To close, I would like to extend a big thank you for our Editorial Board, peer reviewers, interviewees, and contributors who have once again helped to bring together an issue with content of great quality. We look forward to next year's meeting and we hope that you enjoy reading this issue.

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Foreword

Dear Colleagues,

Welcome to our latest issue of *EMJ Rheumatology*, featuring a range of peer-reviewed articles, interviews with key rheumatology experts, and features highlighting the latest advancements in the field of rheumatology. This issue also contains a review of the European Alliance of Associations for Rheumatology (EULAR) 2023 Congress, which was held in Milan, Italy, from 31st May–2nd June. The review offers a detailed overview of the most significant highlights and content presented throughout the congress.

The Editor's Pick in this issue is a paper by de Figueiredo et al. on Sjögren's syndrome research, highlighting the issues on quality of life and nutritional status in patients.

EMJ had the pleasure of speaking to various field experts, namely Denis Poddubnyy, who shared valuable perspectives on unmet needs within rheumatology and potential strategies to tackle them in the future. Furthermore, Christine Peoples shed light on the transformative potential of telemedicine in revolutionising the field. Thomas Huizinga discussed the pathogenesis, early detection, and treatment of rheumatoid arthritis and systemic lupus erythematosus (SLE).

Additionally, Chris Wincup provided in-depth perspectives on SLE, along with insights into their ongoing research projects.

The articles in this issue cover a range of topics. Bennett et al. review bisphosphonate-related osteonecrosis of the jaw in patients with osteoporosis. De Figueredo et al. provide insight into how xerostomia impacts food choice for patients with primary Sjögren's syndrome.

Further content includes an infographic exploring the epidemiology and clinical manifestations of SLE. SLE is a great mimicker of other diseases; therefore, it can be difficult to diagnose. As a result of this, proper and extensive rheumatology training is extremely important in order to understand the full gamata of clinical manifestations of this disease.

As Editor-in-Chief, I would like to thank all the authors, reviewers, and Editorial Board members who contributed to the success of this 2023 issue of EMJ Rheumatology. I hope this journal will continue to extend your boundaries of medical science and disease management and be a valuable resource in your daily clinical practice.

Ian C. Chikanza

Catholic University of Zimbabwe, Harare, Zimbabwe; and University of Zimbabwe, Harare, Zimbabwe

EULAR 2023

Review of the European Alliance of Associations for Rheumatology (EULAR) Congress 2023

Location:	Milan, Italy
Date:	31st May–3rd June 2023
Citation:	EMJ Rheumatol. 2023; DOI/10.33590/emjrheumatol/10300407. https://doi.org/10.33590/emjrheumatol/10300407.

There are over 200 different rheumatic and musculoskeletal conditions, affecting 20–30% of European adults' health, everyday activities, and quality of life. The European Alliance of Associations for Rheumatology (EULAR)'s vision is to create a world where these diseases are recognised, diagnosed, and prevented or cured. Through awareness, education, clinical care, prevention, research, and global solutions for managing these diseases, EULAR aims to minimise the impact of these diseases on individuals and societies. The yearly congress brings together rheumatology experts, health professionals, and people with rheumatic and musculoskeletal disease, offering a chance to share ideas, network, and learn.

Following EULAR's significant achievements in the last few years, the society is now the leading provider in education in rheumatic and musculoskeletal diseases, and has already established a novel infrastructure and governance workflow to continue delivering strategic objectives. This new strategy is built on the tradition and experience of the previous strategy, and the society has established a number of values to ensure the implementation of this, including innovation, patient centredness, responsibility, inclusivity, flexibility, and dedication. At the opening ceremony, EULAR President Annamaria Iagnocco introduced this novel strategy, driven by four directions of impact. Firstly, EULAR prioritises leadership, scientific guidance, and innovation, in an effort to push boundaries and make breakthroughs. As a leading organisation in the field, EULAR is a trusted source of information that can have a great impact on the lives of patients through evidence-based data and advocating for patient-centred care. Secondly, the society is committed to investing in personal and professional development, which will help individuals and teams to thrive. As the leading provider for career progression and professional and personal development in rheumatology, EULAR sets the standards, with a comprehensive view of education, as well as personal development in general. Thirdly, EULAR is building a sustainable and strong community, in which everyone can contribute and be heard. The human connections are integral to the society's culture, which combines people from many countries and backgrounds, and resonates with them not only professionally, but also emotionally. And finally, the society is creating a more equitable and prosperous environment, ensuring that all efforts lead to a viable income. This involves reducing financial risks through diversification of sources of income, ensuring the establishment of a strong source of income.

At the opening ceremony, several awards were presented to people who have been judged by

the EULAR executive committee to have served the rheumatology field in an outstanding way through research, clinical science, or other activities. The Meritorious Service award was presented to Bernard Combe, Centre Hospitalier Universitaire (CHU) Montpellier, France; and Angela Zink, former head of the Programme Area Epidemiology and Health Services Research, German Rheumatism Research Centre (DRFZ), Berlin, Germany. Honorary membership was awarded to individuals who have rendered outstanding service in accomplishing EULAR's objectives, including Thomas Dörner, Charité Universitätsmedizin Berlin, Germany; Jean Dudler, Hôpital Cantonal de Fribourg (HFR), Villars-sur-Glane, Switzerland; Ricardo Ferreira, Centro Hospitalar e Universitário de Coimbra, Portugal; Espen Haavardsholm, University of Oslo, Norway; Janet Pope, University of Western Ontario, London, Canada; Zoltan Szekanecz, University of Debrecen, Hungary; Yoshiya Tanaka, University of Occupational and Environmental Health, Fukuoka, Japan; and Mohammed Tikly, University of the Witwatersrand, Johannesburg, South Africa. The PARE Outstanding Award was presented to Dieter Wiek, Deutsche Rheuma-Liga, Bonn, Germany. The Stene Prize winner was Shauna O'Connor, Trinity College Dublin, Ireland. Finally, the FOREUM 2023 Platinum recognition was awarded to Isabelle Logeart, Pfizer, France.

Over 4,500 abstracts were submitted and reviewed by over 250 reviewers in order to select the best research to be presented at the congress. The congress further offered a multitude of opportunities that were designed to promote education, collaboration, innovation, and success. EMJ was delighted to attend this insightful congress, and cannot wait for the next one in Vienna, Austria, from the 12th–15th June 2024. Read on for scientific highlights from the congress, covering topics such as the role of artificial intelligence in early rheumatoid arthritis, and factors associated with delayed diagnosis of familial Mediterranean fever.

Systemic Lupus Erythematosus Associated Hypertension: New Insights

PULMONARY arterial hypertension (PAH) is a severe manifestation of both systemic sclerosis (SSc) and systemic lupus erythematosus (SLE). Previous research has described improved survival in SSc-associated PAH, while research into SLE-associated PAH is limited. A team from Peking Union Medical College Hospital, Beijing, China, therefore sought to explore the changes in characteristics, 5-year survival, and treatment for SLE-associated PAH over the last decade.

The multicentre, prospective cohort study included 610 patients with SLE-associated PAH. The cohort was divided into two test groups depending upon the date that the patient underwent right heart catheterisation. Cohort A covered 2011–2016, and B 2016–2021. In tandem, a single-centre cohort of 104 patients with idiopathic pulmonary arterial hypertension acted as the control group. Primary outcomes investigated were treatment regimen, disease characteristics, and all-cause mortality.

Analysis of demographic data revealed that SLE PAH patients were overall younger, predominantly female, had lower levels of an important cardiac biomarker (NTproBNP), better haemodynamics, and a higher 5-year survival rate than patients with PAH. When comparing the two patient cohorts, B showed lower mean pulmonary arterial pressure and pulmonary vascular resistance. Cohort B also demonstrated a higher 5-year survival rate (88%) than cohort A (72.9%), and was more likely to receive intensive immunosuppressants and PAH-targeted medication. Further analysis into the possible reasons for the differences in survival showed that treatment goal achievement in PAH and reaching lupus low disease activity state were both independently associated with lower mortality.

"The multicentre, prospective cohort study included 610 patients with SLE-associated PAH."

Overall, this study is the largest multicentre prospective study investigating an SLE-PAH cohort to date. Results suggest survival has improved significantly for SLE-associated PAH; however, the importance of early detection of PAH in patients with SLE, and the importance of achieving treatment goals for both patients with PAH and SLE remains. ●

Rheumatic and Musculoskeletal Diseases Frequently Advance Lethal Comorbidities

RHEUMATIC and Musculoskeletal Diseases (RMD) encompass over 200 diseases, which affect more than 120 million Europeans of all ages. RMDs have a significant direct impact on patients, but also most RMDs pose a further significant risk to the population by advancing many comorbidities, if the RMD is not correctly treated.

Cardiovascular disease, lung disease, cancers, gastrointestinal disease, and mental health disorders are examples of the most significant comorbidities of inflammatory RMDs. Most of these comorbidities are prioritised by the European Union (EU) as key non-communicable diseases, focused on by initiatives such as the Beating Cancer Plan and the Healthier Together – EU Non-Communicable Diseases (NCD) Initiative. However, RMDs are commonly ignored in healthcare policies, as it is incorrectly assumed that they have a low mortality rate. The discovery of novel medications and mechanisms of disease have advanced our understanding of the correlation between inflammatory RMDs and these comorbidities.

RMDs comprise much of the rapidly increasing emergence of multi-morbidity, because patients with RMDs commonly pass away from the associated comorbidities. Unfortunately, the treatment of RMD is often neglected when multiple diseases coexist in the same patient and, along with the complications of reduced physical activity due to pain and uncontrolled inflammation, this all amounts to an even worse quality of life. Consequently, it is important to educate both policymakers and other medical specialities about RMDs, as well as to improve collaboration for better chronic disease care.

If the underlying conditions are not addressed, then the comorbidities of RMDs can be triggered, often leading to uncontrolled inflammation affecting other organs. For instance, one in five cancers is caused or promoted by inflammation, and RMDs increase the risk of heart attacks by 63 (rising to 98% in patients with lupus).

Evidently, the relationship between RMDs, the immune system, inflammation, and comorbidities is complex and multifaceted, as represented by the abstracts presented at the European Alliance of Associations for Rheumatology (EULAR) Congress 2023. Resultingly, EULAR calls upon the EU to generate an approach to tackle RMDs and reduce their comorbidity risk, as well as repurpose RMD drugs to remedy other diseases. Hence, further research is required to elucidate the emergence in multi-morbidity. ●

"RMDs are commonly ignored in healthcare policies, as it is incorrectly assumed that they have a low mortality rate."

Healthy Lifestyle for Reduced Mortality in Osteoarthritis

LEADING a healthy lifestyle is a widely accepted mitigator for mortality. New data relating to osteoarthritis from a prospective cohort study was presented at the European Alliance of Associations for Rheumatology (EULAR) Congress 2023.

This research investigated the association of individual and combined healthy lifestyle factors with risk of all-cause and cause-specific mortality in 104,142 patients with osteoarthritis. Findings from this work inform the effect of several lifestyle factors on reducing mortality in osteoarthritic populations, where most previous study is broadly conducted on the general population.

Data was provided by the UK Biobank, and the cohort under scrutiny experienced 9,915 deaths in the first 2 years of follow-up. The researchers gave each participant a score for their lifestyle, based on BMI and self-reported diet, sleep duration, physical activity, sedentary time, social connection, smoking, and alcohol consumption. The statistical models produced showed variety in their associations between lifestyle and mortality: sleep duration had a U-shaped relationship; meanwhile, moderate physical activity was L-shaped, and both BMI and vigorous physical activity were J-shaped, starting with a sharp drop followed by dramatic rise. Looking at the results, the lowest risk of mortality was seen with 7 hours of sleep a night, and the turning points for moderate and vigorous physical activity were 550 minutes and 240 minutes per week, respectively. The turning point for BMI was recorded as 28 kg/m^2. Using multivariable models, each lifestyle factor was significantly associated with all-cause mortality, and mortality associated with cancer, cardiovascular, digestive, and respiratory diseases.

These findings are expected to guide lifestyle choices and further research, proving important by identifying the patterns to follow in order to reduce risk of mortality in osteoarthritic and other sub-populations. The underlying message in this study centres on the importance of a healthy lifestyle, how these modifications should be implemented, and the role this will have on patient health; optimistically, individuals will experience better disease outcomes alongside reduced risk of mortality.

"Data was provided by the UK Biobank, and the cohort under scrutiny experienced 9,915 deaths in the first 2 years of follow-up."

Understanding Diagnostic Delay in Familial Mediterranean Fever

FINDINGS from a study investigating the factors associated with delayed diagnosis in familial Mediterranean fever (FMF) were presented during a scientific session that took place at the European Alliance of Associations for Rheumatology (EULAR) Congress 2023, in Milan, Italy, on 31st May. This is the first large European cohort study investigating the factors associated with diagnostic delay in FMF, according to the authors.

The study enrolled 960 patients with FMF using data from the Juvenile Inflammatory Rheumatism cohort. FMF is the most common autoinflammatory condition globally, and is associated with mutations in *MEFV*. It involves recurrent, short-lived (<3 days) attacks of fever alongside chest or abdominal pain. Due to reports from several studies that diagnosis is often missed or delayed, even in countries of high prevalence, the study aimed to identify the frequency and factors associated with diagnostic delay.

Data analysis showed that one-fifth of patients experienced a diagnostic delay, defined as diagnosis >10 years after symptom onset. Rates of diagnostic delay were found to be higher in females than males, and patients who experienced delayed diagnosis were found to have an older median age compared to the remaining 80% of the cohort, at 46.4 years and 15.5 years, respectively.

Regarding clinical presentation during disease attacks, the authors found no difference in abdominal pain, chest pain, or musculoskeletal symptoms between those with a diagnostic delay and those without. However, those with delayed diagnosis did display higher rates of erysipelas-like erythema. This pathognomonic feature of FMF occurred in 33% patients with delayed diagnosis, compared to 22% in those diagnosed within 10 years of symptom onset. Additionally, amyloidosis was identified as being significantly higher amongst individuals with a delayed diagnosis compared to those without, and those with delayed diagnosis received significantly more biotherapy.

"One-fifth of patients experienced a diagnostic delay, defined as diagnosis >10 years after symptom onset."

The study also evaluated *MEFV* mutations between those with and without a delayed diagnosis, and found that there were no differences in the percentage of patients with either one or two pathogenic mutations in this gene.

The findings from this study highlight the need for improved education surrounding FMF, and improved communication to clinicians and patients to help reduce delays in diagnosis.

How Does COVID-19 Affect Patients with Rheumatic Diseases?

LONG-TERM consequences of COVID-19 in people with rheumatic and musculoskeletal diseases were discussed in multiple sessions at the European Alliance of Associations for Rheumatology (EULAR) Congress 2023. Currently, data on long COVID in patients affected by inflammatory diseases (iRD) are scarce, heterogeneous, and largely inconclusive. Furthermore, it is often hard to differentiate which symptoms are attributable to iRD, compared to long COVID.

A Dutch study presented at the congress looked into the risk of developing long COVID after infection with the Omicron variant in patients with iRD, compared to healthy age- and sex-matched controls. In total, 1,974 patients with iRD participated in the study, as well as 733 healthy controls, 24% and 30% of whom were infected with the Omicron variant, respectively. There were more patients with iRD who fulfilled criteria for long COVID compared to healthy controls; however, these results were attenuated after adjusting for potential cofounders.

The team noted that more patients with iRD without a history of COVID-19 reported iRD, compared to healthy controls; however, this could be due to clinical manifestations of underlying rheumatic diseases. The team concluded that patients with iRD are not more likely to develop long COVID than the general population.

Another session looked at whether anti-Spike antibody levels after vaccination could predict breakthrough infection and clinical outcome of COVID-19 in patients with immune-mediated inflammatory disease on immunosuppressive therapies. In total, 1,051 patients provided samples after receiving three vaccine doses, as well as responding to a follow-up questionnaire. Half of the patients reported COVID-19, but few had life-threatening illness. Those with the highest anti-Spike levels were at a lower risk of COVID-19 infection, which supports the use of vaccination in this patient group. The team concluded that low antibody levels did not increase the risk of severe COVID-19, as shown by the absence of severe infections and deaths.

Finally, a study on the safety of COVID-19 vaccines in pregnant and breastfeeding females with autoimmune diseases was presented. A total of 40 pregnant patients were included, with a vaccination rate of 100%, as well as 52 breastfeeding patients, with a vaccination rate of 96.2%. Of the pregnant participants, 71.5% reported post-vaccination disease flares, compared to 20% of those breastfeeding, and 18% of age- and disease-matched control patients. A change in immunosuppressive treatment was necessary in one in five patients. The authors concluded that while pregnant individuals reported adverse events more often than those who were breastfeeding, they were not higher than in healthy controls. ●

"1,974 patients with iRD participated in the study, as well as 733 healthy controls, 24% and 30% of whom were infected with the Omicron variant."

Novel Data Demonstrates Autoimmune Disorders Affect One in Ten

NEW data presented at the European Alliance of Associations for Rheumatology (EULAR) Congress 2023 in Milan, Italy, highlighted that autoimmune disease affects one in 10 people, an increase in incidence possibly linked to environmental factors. Experts stressed that there is a lack of currently available data, and that the level of understanding about disease trends between individuals is currently poor.

"Autoimmune disorders are commonly associated with each other, particularly Sjögren's [syndrome], systemic lupus erythematosus, and systemic sclerosis," stated Nathalie Conrad, Department of Public Health and Primary Care, Katholieke Universiteit Leuven (KUL), Belgium. "Patients with Type 1 diabetes also have significantly higher rates of Addison's, coeliac, and thyroid diseases, and multiple sclerosis stands out as having low rates of co-occurrence with other autoimmune diseases."

The novel data comes from a new population-based study including over 22 million people, which aimed to address the lack of reliable estimates for prevalence and incidence of autoimmune diseases. Conrad and their team investigated the 19 most common autoimmune diseases and examined trends over time, analysing sex, age, economic status, season, and geography against incidence. Analysis of the electronic health records of 22 million people in the UK found that between 2000–2009, a novel diagnosis of autoimmune disease was made in 968,872 people. When considered together, the 19 autoimmune disorders impacted 10.2% of the population, 13.1% of females and 7.4% of males.

"The novel data comes from a new population-based study including over 22 million people."

Additionally, the researchers analysed the age-standardised incidence rates of autoimmune disease throughout the study period, and found an increase of 4%. The largest increases were identified in Graves' disease, coeliac disease, and Sjögren's syndrome. They also identified a significant decrease in the incidence of both Hashimoto's thyroiditis and pernicious anaemia. Socioeconomic gradients were identified in several diseases, and seasonal variations were noted in Type 1 diabetes and vitiligo diagnosis. Several regional variations were also noted. ●

Can Artificial Intelligence Accurately Predict Rheumatoid Arthritis Development?

DEEP-LEARNING artificial intelligence (AI) can analyse MRI scans automatically to predict early-stage rheumatoid arthritis (RA), according to research presented at the European Alliance of Associations for Rheumatology (EULAR) Congress 2023.

While early inflammatory arthritis is often undifferentiated, it can develop into established RA or another arthropathy. Traditionally, rheumatologists and radiologists would manually identify key features of the condition from MRI scans of hands and feet.

MRI is used to detect erosion in the joints, which is a key prognostic factor, and allows rheumatologists and radiologists to see and assess bone marrow oedema and (teno-) synovitis. Its use is essential in predicting early RA, allowing patients to access timely treatment, and potentially changing the course of their disease.

To determine whether deep-learning AI could predict early-stage RA, Y. Li, Division of Image Processing, Department of Radiology, Leiden University Medical Center (LUMC), the Netherlands, and colleagues trained an AI model to understand anatomy. Then, it was trained to distinguish healthy controls from patients with clinically suspect arthralgia, and to find features that predict rheumatoid arthritis development.

Once the AI had finished its training, it analysed scans of 1,974 patients with clinically suspect arthralgia or early-onset arthritis. Much like the traditional, manual method, the AI model looked at MRI scans of the hands and feet. Of the 1,974 patients, 651 developed RA, with the AI model predicting RA development with accuracies close to that achieved by the rheumatological and radiological experts.

> **"MRI is used to detect erosion in the joints, which is a key prognostic factor."**

While further training with healthy controls is needed to improve accuracy, Li and colleagues concluded that AI can accurately interpret MRI scans to provide RA prediction automatically. The AI model also confirms the significance of inflammatory features, such as synovial inflammation, in RA, and it is possible that it could identify new imaging biomarkers that further enhance understanding of the underlying disease process of early RA.

Rheumatoid Arthritis and Cardiovascular Disease

NEW data presented at the European Alliance of Associations for Rheumatology (EULAR) Congress 2023 looked at the risk of cardiovascular disease in patients with rheumatoid arthritis (RA). These patients have an increased risk for cardiovascular disease, including acute coronary syndromes (ACS), compared to the general population. Treatment with disease-modifying antirheumatic drugs may benefit them, as this risk is mediated by systemic inflammation; however, the extent of this benefit remains unknown.

Researchers followed patients with RA treated with either methotrexate or tumour necrosis factor inhibitors for 1 year between 2020–2021. In total, 40% of people treated with MTX, and 32% of those treated with TNFi, achieved remission. Both groups had a similar risk of ACS, and the incidence rate of ACS of patients in remission were similar to that in the general population.

The team also analysed the impact of cardiovascular comorbidities on the efficacy of both treatments, using data from the ORAL Surveillance study. The 4,362 participants all had RA and at least one additional cardiovascular risk factor. They were categorised based on history of atherosclerotic cardiovascular disease (HxASCVD). Of these patients, 640 had a HxASCVD, and 3,722 did not. The efficacy of tofacitinib was at least as good as TNFi in those without HxASCVD, and risk of major adverse cardiovascular events (MACE) was similar. Patients who had an intermediate or high cardiovascular risk score, or low–borderline risk scores, were more likely to reach low disease activity with tofacitinib compared to TNFi.

Lead author Maya Buch, University of Manchester, UK, stated: “Overall, these findings further characterise the benefit–risk of tofacitinib by cardiovascular risk category, and provide a means to risk-stratify patients, such that tofacitinib can be considered an effective treatment option where appropriate.”

"There was no significantly higher risk of MACE in those treated with TNFi compared to JAKi."

An abstract presented by Romain Aymon, Geneva University Hospitals, Switzerland, considered the incidence of MACE in patients treated with bDMARDS compared to janus kinase inhibitors (JAKi). This study included patients starting TNFi, JAKi, or bDMARDs with other modes of action (50,325 treatment initiations in total). All participants had one or more cardiovascular risk factor. In total, 182 incident MACE were reported; however, there was no significantly higher risk of MACE in those treated with TNFi compared to JAKi. Furthermore, adjusted regression analysis did not show a significant difference in MACE incidence between other modes of action versus TNFi, and JAKi versus TNFi. The team is planning to include other registers in order to increase statistical power and evaluate other adverse events, including cancers, thromboembolic events, and serious infections. ●

Elevated Risk of Cardiovascular Disease in Patients with Psoriatic Arthritis

EVIDENCE from a new study, presented at the European Alliance of Associations for Rheumatology (EULAR) Congress 2023 in Milan, Italy, has demonstrated a link between patients with psoriatic arthritis (PsA) and an elevated risk of contracting cardiovascular disease. Researchers discovered that aortic vascular inflammation is more common in patients with active PsA when compared with a control group.

The retrospective study and meta-analyses, which was carried out at the University Medical Center (UMC) Utrecht, the Netherlands, aimed to investigate if patients with moderate to severe PsA have increased vascular inflammation when compared to the general population. The study included a group of 75 patients with PsA (median age: 53, and median swollen joint count: 3) who had active peripheral arthritis (≥2 swollen and tender joints), and compared them to 40 individuals with melanoma, none of whom were receiving immunotherapy, or had distant metastases, the chosen non-inflammatory controls. All patients and controls were aged between 18–75. Clinical disease activity used measures of assessment including body surface area, joint counts, and the Disease Activity Index for PsA.

Target-to-background ratio PET and CT scans, a reliable and reproducible measure of inflammation, demonstrated that vascular inflammation was elevated in those with PsA (mean target-to-background for entire aorta: 1.53±0.15 and 1.42±0.13, respectively; P<0.001). Data were found to be significant after adjustment to account for the impacts of body mass index, mean arterial pressure, age, and sex.

Researchers found that increased vascular inflammation remained consistent across different components that were measured in the study, including the infrarenal aorta, suprarenal aorta, ascending and descending aorta, and aortic arch (P=0.002). Spearman's correlation coefficient was utilised to assess vascular information and the disease activity's clinical parameters.

No significant differences were observed between patients with PsA and the control group with regard to age, mean arterial pressure, and history of cardiovascular disease. However, patients with PSA were found to have a higher BMI when compared to the control group.

Lead author Nienke Kleinrensink, Department of Internal Medicine and Dermatology, UMC Utrecht, commented: "This evidence suggests that inflammation in PsA is not limited to skin and joints, but also involves the cardiovascular system." ●

"Clinical disease activity used measures of assessment including body surface area, joint counts, and the Disease Activity Index for PsA."

Difficult-to-Treat Disease in Rheumatology

Authors: Darcy Richards, Editorial Assistant

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THE CHALLENGE of difficult-to-treat disease in rheumatology was explored during an insightful clinical science session at the European Alliance of Associations for Rheumatology (EULAR) 2023 Congress, which took place in Milan, Italy, between the 31st May–3rd June. The session, entitled 'Everything is difficult to treat?', explored key elements that contribute to the challenge in treating rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc).

INTRODUCTION

The session was chaired by Jacob M. van Laar, University Medical Center Utrecht, the Netherlands, and László Czirják, Medical School, University of Pécs, Hungary. Whilst the experts discussed different rheumatological conditions, they highlighted several recurring themes, as well as disease-specific challenges that contribute to treatment difficulty.

DEFINING 'DIFFICULT-TO-TREAT'

Defining 'difficult-to-treat' across these four conditions is challenging. There are some cross-applicable characteristics alongside disease-specific features. This, compounded by challenges in accurate or delayed diagnosis, can muddy the water in terms of defining if a disease is in fact difficult-to-treat or not.

György Nagy, Semmelweis University, Budapest, Hungary, discussed the EULAR definition for difficult-to-treat RA, which is based upon three criteria. The first criterion is failure of ≥2 biologic/targeted synthetic (b/ts) disease-modifying antirheumatic drugs (DMARD) with different mechanisms of action, after failing treatment with conventional synthetic (cs) DMARD therapy (unless contraindicated).

The second is the presence of signs suggestive of active or progressive disease, defined as ≥1 of the following: at least moderate disease activity according to validated composite measures, such as DAS28-ESR >3.2 or CDAI >10; signs and/or symptoms suggestive of active disease; inability to taper glucocorticoid treatment to <7.5 mg/day of prednisone or equivalent; rapid radiographic progression, with or without signs of active disease; and RA symptoms causing a reduction in quality of life. The third and final criterion is the management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or patient.

In the absence of a specific definition for axSpA, SSc, or SLE, Mariusz Korkosz, Jagiellonian University Medical College and University Hospital, Kraków, Poland, explored whether the EULAR definition for RA can be applied to axSpA. Criteria one and three can be extrapolated to apply to axSpA, Korkosz confirmed. However, criterion two requires adjustments to be applicable. Rapid radiographic progression is not applicable to axSpA, and the inabilityto taper glucocorticoid treatment would need to be changed to the inability to reduce or discontinue non-steroidal anti-inflammatory medication.

WHAT MAKES THESE CONDITIONS DIFFICULT TO TREAT?

Common themes, including comorbidities, treatment failure, and treatment adherence were, discussed across the expert presentations.

David Isenberg, University College London, UK, highlighted that whilst survival has improved, 15% of patients with SLE die within 15 years of diagnosis. Isenberg explored the four key factors that make SLE a difficult disease to treat.

Firstly, Isenberg stated: "Lupus is truly the great mimic," and showcased the numerous ways in which lupus can manifest. This clinical heterogeneity, in turn, can impair the ability to make the diagnosis quickly, and without accurate diagnosis the appropriate treatment will inevitably be delayed.

Furthermore, Isenberg explained that SLE is unpredictable, and whilst there are three distinct patterns of disease, these do not cover disease trajectories in all patients, and only 15% of patients achieve complete remission. Isenberg also commented that limitations of current therapeutics also contribute to the difficulty in treating SLE.

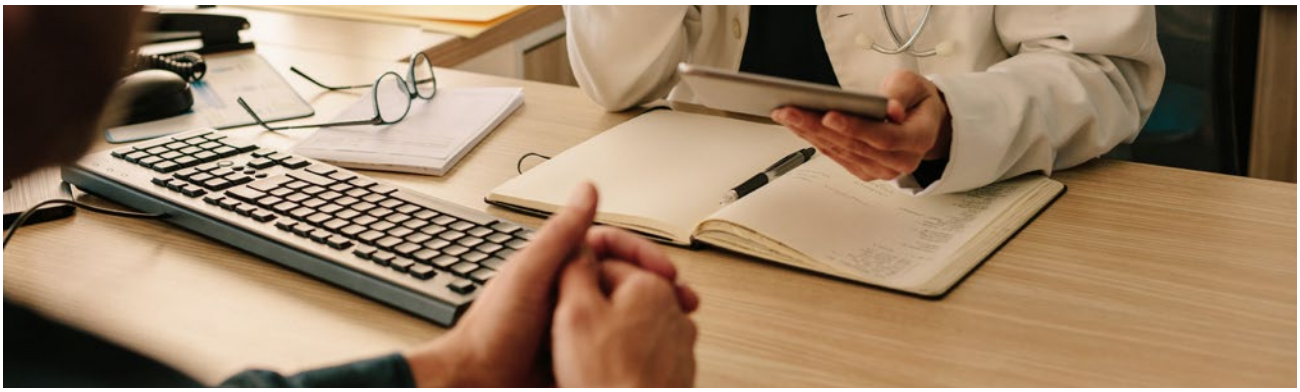
In relation to the latter, Isenberg discussed how the options available to treat SLE after conventional treatment failure are limited, which is not the case for other rheumatological conditions. However, they did express hope for the future with new biologics in development, and the potential role for chimeric antigen receptor (CAR) T-cell therapy.

Additionally, Isenberg discussed comorbidities as a factor in difficult-to-treat disease. Up to 30–40% of patients with lupus will have other autoimmune disease diagnoses. Such comorbidities add to the complexity of disease management, thus contributing to treatment difficulty. Other scenarios that pose treatment difficulty, including aggressive lupus nephritis, lupus psychosis, SLE plus anti-phospholipid syndrome, and SLE plus infection, were also considered in further detail.

Comorbidities were also discussed in the other expert presentations. Nagy commented that 10% of patients with RA are difficult to treat in clinical practice, and explored the factors associated with difficult-to-treat RA, highlighting comorbidities, behavioural and lifestyle factors, rapid radiographic progression, and disease refractory to glucocorticoid and/or DMARD therapy as key contributors.

Nagy also explored the role of pain and inflammation in difficult-to-treat RA, highlighting a study assessing the relationship between pain and inflammation in difficult-to-treat disease compared with healthy controls. Preliminary data from this study have shown that right and left postcentral gyrus connectivity

"Common themes, including comorbidities, treatment failure, and treatment adherence, were discussed."



strength drops following pain stimuli in patients with difficult-to-treat disease, compared to no change in connectivity in healthy controls, Nagy explained. This data was statistically significant and reproducible. However, further work is required to elucidate these pathways further, and investigate their potential in managing difficult-to-treat RA.

In terms of axSpA, Korkosz also highlighted comorbidities as a characterising feature for difficult-to-treat disease. Alongside this, it was explained that extra-musculoskeletal and peripheral disease manifestations, clinical heterogeneity, structural damage, and patient expectations also play a role in difficult-to-treat disease.

Regarding SSc, Gabriella Szücs, University of Debrecen, Hungary, highlighted complex pathogenesis; lack of gold standard for assessment of disease activity, which makes it difficult to identify those at risk of early progression; and, in agreement with Isenberg, commented how diagnostic delays, clinical heterogeneity, and limited treatment options contribute to the difficulty in treating the disease. Szücs explained how the different potential organ manifestations of SSc mean that there is no single treatment strategy that can be applied to patients with SSc. They further discussed how several of these organ manifestations are very difficult to treat, spotlighting interstitial lung disease, pulmonary arterial hypertension, digital vasculopathy, calcinosis, gastrointestinal symptoms, and cardiac disease.

FUTURE DIRECTIONS FOR DIFFICULT-TO-TREAT DISEASE

When exploring ideas for future directions, the experts discussed the importance of prognostic factors in predicting difficult-to-treat disease; the need for translational research and clinical trials to optimise new therapeutics and therapeutic targets; the potential role of artificial intelligence to develop predictive algorithms; developing disease-specific definitions and guidance for difficult-to-treat disease; and for SLE specifically, the potential for, and outcomes of, studies investigating the use of CAR T-cell therapy.

CONCLUSION

Difficult-to-treat disease is complex, and management requires the consideration of several contributing factors that are both patient- and non-patient related. The approach to management should be multifactorial, and involve a combination of pharmacological and non-pharmacological strategies. Working towards improved time to and accuracy of diagnosis, risk prediction, and optimisation of comorbidities are key challenges involved in the management of difficult-to-treat disease. Future efforts should focus on translational research and clinical trials, novel therapeutic options, personalised treatment pathways, and the development of clear definitions and guidelines to aid clinicians in the management of difficult-to-treat rheumatological diseases.

"Diagnostic delays, clinical heterogeneity, and limited treatment options contribute to the difficulty in treating the disease."

Precision Medicine in Systemic Lupus Erythematosus

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A session on precision medicine in systemic lupus erythematosus (SLE) took place at the European Alliance of Associations for Rheumatology (EULAR) 2023 meeting in Milan, Italy, merging one of the most contemporary topics in modern healthcare with an important subject in the rheumatology specialty. Co-chaired by Dimitrios Boumpas, University of Athens, Greece, and José Pego-Reigosa, University Hospital Complex of Vigo, Spain, this series of presentations was among the most highly attended, and featured cutting-edge insights from front-running experts on lupus.

MOLECULAR MECHANISMS AND HETEROGENEITY

Spotlighting heterogeneity, unpredictability, and difficulties with early diagnosis, Marta Alarcón-Riquelme, Pfizer-University of Granada-Junta de Andalucía Centre for Genomics and Oncological Research (GENYO), Spain, drew attention to the three pillars healthcare professionals face in precision medicine for SLE and other autoimmune diseases. Alarcón-Riquelme exhibited the research that they have led on reclassifying systemic autoimmune diseases, regardless of their clinical diagnosis. This utilised PRECISESADS, a study that has gathered data on SLE, amongst other autoimmune conditions, such as rheumatoid arthritis, Sjögren's syndrome, and systemic sclerosis.

Using molecular patterns to predict flares or long-term remission is an avenue that shows promise; findings have shown that the speed of reduction in dysregulation of some gene expression modules using neutrophils, platelets, plasma cells, and erythrocyte modules can predict long-term remission. Alarcón-Riquelme noted that interferons are not good predictors of remission due to their slow rates of disappearance, but explained that close to a flare, there is a high probability of finding platelet and erythrocyte modules, and this can be used to forecast, thus tackling unpredictability.

This research also investigated which types of cells differentiate patients belonging to separate transcriptome groups, and how these differ on a single cell level when responding or not responding to therapy.

Alarcón-Riquelme went on to discuss the European 3TR project, which they currently co-ordinate. It examines the mechanisms of known response to treatment across multiple diseases, including SLE. The question that this research aims to answer is if molecular patterns can predict therapeutic responses and mechanisms of no response across these diseases, which would improve diagnosis and further our understanding.

Next steps in this field involve identifying molecular patterns of response and non-response, identifying protein markers for drugs that follow the behaviour of these molecular patterns, and how to directly translate applications of these patterns into clinical practice.

CLASSIFICATION AND DIAGNOSIS

Martin Aringer, University Medical Center Carl Gustav Carus, Technische Universität Dresden, Germany, began by highlighting the requirement for high specificity when defining classification criteria.

Aringer presented the EULAR/American College of Rheumatology (ACR) criteria for SLE and highlighted differences when compared with other systems, such as with using antinuclear antibodies as an entry criterion. "Lupus is not a particularly uniform disease, and that is one of the challenges we face," was the way Aringer described the variability and complexity of lupus as a condition, which harbours difficulties with classification and diagnosis. A barrier to consider when looking at translating these parameters into practice is feasibility, which can be an issue when deciding on what criteria that will work worldwide; it is because of this that some criteria have been left out at this stage.

"Lupus is not a particularly uniform disease, and that is one of the challenges we face."

Turning to molecular stratification, Aringer explained that distinct differences, from a clinical point of view, allow classification into subsets of SLE as a disease entity and guide therapy selection for patients. However, these groups are not specific enough to clarify between diseases at present. Using graphs to compare SLE and Sjögren's syndrome, an area that is always difficult to classify, Aringer highlighted overlaps in molecular group measurements, and reassured the audience that there are ways to differentiate, such as comparing interferons. The information from this presentation demonstrated that molecular grading is good and improving, but clinical diagnosis is still better at present, and moving forward, these branches should be used in conjunction.

Concluding, Aringer emphasised the complexity and one of the main challenges associated with the precision approach to lupus classification and diagnosis, stating that any patient with lupus "may have any symptom combined with any other; there is not a fixed combination."

IDENTIFYING THE RIGHT THERAPY

Acknowledging that there is a growing problem in choosing between all the available therapies with different mechanisms of action, Edward Vital, University of Leeds, UK, focused on drugs that are close to being in the clinic, or are already there. Beginning by comparing selection of belimumab and anifrolumab for non-renal SLE, Vital discussed the usefulness of existing biomarkers in a precision approach for existing therapies.

Vital provided three ways in which biomarkers are helpful in stratifying SLE trials: identifying individuals with active disease, predicting flares and remissions, and highlighting the presence of immune endotypes. Plasmablasts were one of the biomarkers under question; not directly killed by rituximab, and with a short lifespan in circulation, it is a possible indicator of B cell activity at other sites. Shifting to discuss rituximab, Vital explained that "one of the issues with rituximab is that it does not deplete B cells as well as we initially thought." This presentation clarified that complete B cell and plasmablast depletion predicts better clearance of autoantibodies and clinical response for therapies, a helpful idea to guide future precision approaches. Vital described the effectiveness of new Type 2 monoclonal antibodies killing B cells directly, providing better B cell depletion, and touched on the promising emergence of chimeric antigen receptor-T mechanisms that reprogramme a patient's T cells to target B cells.

"One of the issues with rituximab is that it does not deplete B cells as well as we initially thought."

Delving deeper into precision initiatives for SLE, Vital questioned if killing B cells more intensively is the correct approach. Although B cell depleting therapies are useful for physicians and patients, patterns of relapse have been found dependent on the proportion of returning plasmablasts.

"It seems to me this is not a function of how well the B cells were killed in the first place; rather, it is a function of the immune environment into which they return," was the explanation Vital provided, simplifying things to: "Lupus is in the soil."

Presenting a problematic case of cryoglobulinaemia from their own clinic, Vital concluded by describing a successful approach that targeted plasma cells directly ahead of B cells, resulting in complete remission with no further therapy 8 years on. This plasma targeting mechanism is undoubtedly an important option for patients with B cell-independent and antibody-dependent disease.

Coming full circle, Vital provided advice for physicians struggling with therapy selection, and described the case that first sparked their interest in lupus, involving interferon activity that results in antiviral and immunostimulatory responses. Vital emphasised the complex processes involved in lupus, and praised innate immune targeting as a different way of conducting treatment.

CONCLUDING REMARKS

Rounding off the session, Sarah Dyball, University of Manchester, UK, presented the classification criteria for clinical trials as treatment becomes more precise. Dyball warned that a large proportion of patients are excluded from Phase III trials as they do not meet eligible clinical diagnosis or fulfil criteria for an overlap syndrome. New criteria may take several years to be adopted into practice, and Dyball recommended a shift away from classification criteria, instead moving towards a stratified approach using immunopathology, such as molecular stratified basket trials for connective tissue disease.

A consistent theme throughout the session was the great complexity of SLE. Insights provided by the speakers in this session will impact the decision-making of clinicians and guide future research, in turn contributing to further unravelling this intricate and perplexing disease, and resulting in more accurate targeting of precision medicine. ●

"This is not a function of how well the B cells were killed in the first place; rather, it is a function of the immune environment into which they return."

European Alliance of Associations for Rheumatology (EULAR) Congress 2023: Take-Home Messages from an Excellent Congress

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This excellent congress took place between 31st May–3rd June 2023 in the beautiful city of Milan, Italy, featuring the stunning church of Duomo di Milano in the centre of the city. The congress covered all topics of Rheumatology. During the opening plenary session, Annamaria Iagnocco, European Alliance of Associations for Rheumatology (EULAR) President, presented EULAR's new strategy and its key priorities.

RHEUMATOID ARTHRITIS

Daniel Aletaha, University of Vienna, Austria, presented research on the prevention of rheumatoid arthritis (RA), explaining that abatacept may have a role if used early. Drug safety is very important and rheumatologists need to carry out risk/benefit assessments before choosing therapeutic agents. Aletaha mentioned a few new treatments with interesting modes of action/delivery systems, and discussed treatment targets. Comorbidities are relevant in the management of RA and can influence our choice of therapy and its response.

"Drug safety is very important and rheumatologists need to carry out risk/benefit assessments."

LUNG INVOLVEMENT IN AUTOIMMUNE RHEUMATIC DISEASES

Oliver Distler, University of Zürich, Switzerland, presented evidence supporting the use and clinical benefit of the following agents in the management of systemic sclerosis-associated interstitial lung disease: cyclophosphamide, nintedanib, mycophenolate mofetil, tocilizumab, and rituximab. Distler also presented evidence supporting the use and clinical benefit of nintedanib and pirfenidone in the management of RA interstitial lung disease.

OSTEOARTHRITIS THERAPIES

Ruth Wittoek, Ghent University, Belgium, presented data on the successful structure modification in erosive hand osteoarthritis (OA) by denosumab, a RANKL inhibitor. Michelle Heijman, Sint Maartenskliniek, Nijmegen, the Netherlands, presented data suggesting

that colchicine 0.5 mg daily was associated with a lower incidence of total hip and knee replacements as compared with placebo. Timothy McAlindon, Tufts Medical Center, Boston, Massachusetts, USA, presented evidence that lorecivivint 0.07 mg, a CLK/DYRK inhibitor, appears safe and well-tolerated in patients with severe knee OA. There is potential benefit on joint space narrowing at 24 and 36 months, and there are potential benefits on patient reported outcomes. Tuva Moseng, Diakonhjemmet Hospital, Oslo, Norway, presented an update on the EULAR recommendations for the non-pharmacological management of hip and knee OA.

BIOLOGICS FOR RHEUMATOID ARTHRITIS

Andrew Cope, King's College London, UK, presented the results of the APIPPRA study, which demonstrated that abatacept reduces the rate of progression to clinical arthritis or RA during the treatment phase. The study also demonstrated that there are consistent effects on symptoms and patient-reported outcomes during the first 12 months.

Noortje van Herwaarden, Sint Maartenskliniek, Nijmegen, the Netherlands, presented the results of the DRESS study, which revealed that long term disease activity guided dose optimisation of TNF inhibitors in RA results in stable low disease activity, and a 40–50% reduction in TNF inhibitors and other biological disease-modifying antirheumatic drug (DMARD) use.

Discontinuation does not seem to cause long-term disease deterioration, and biologic and targeted synthetic DMARD-free remission for a relevant period of time is possible in a non-negligible number of patients.

AXIAL AND PERIPHERAL SPONDYLOARTHRITIS

Désirée van der Heijde, Leiden University, the Netherlands, presented on the management of spondyloarthritis, highlighting the importance for correct diagnosis and types of manifestations in order to choose the correct treatment strategy. The Assessment of SpondyloArthritis International Society (ASAS)-EULAR recommendations provide guidance to therapy.

SJÖGREN'S SYNDROME

Hendrika Bootsma, University Medical Center Groningen, the Netherlands, presented the clinical phenotype of the disease, the 2016 EULAR/American College of Rheumatology (ACR) classification criteria, and mucosa-associated lymphoid tissue lymphoma in Sjögren's. syndrome They presented clinical trials on

iscalimab (anti-CD40), ianalumab (anti-BAFF receptor), belimumab/rituximab combination, remibrutinib (BTK inhibitor), and stem cell therapy rescue for hyposalivation with positive results.

SYSTEMIC LUPUS ERYTHEMATOSUS

Dimitrios Boumpas, University of Athens, Greece, presented the important features in renal biopsy, i.e., the activity and chronicity features. They stressed the importance of not underestimating haematuria and of having a low threshold for renal biopsy. Haematuria and active urine sediment are reliable indicators for activity and flare. Proteinuria is a good prognostic factor if below 0.7 mg/dL. Boumpas discussed remission and lupus low disease activity state. They presented evidence on the treatment of lupus nephritis, i.e., the similar efficacy of mycophenolate mofetil and cyclophosphamide, and the efficacy of belimumab, voclosporin, and obituzumab. Boumpas also described tapering of therapy in patients with quiescent disease and that steroids should be tapered first. They highlighted that there is no safe dose of steroids for long-term use. Following renal response their team continues treatment of lupus nephritis for at least 3 years.

"There is no safe dose of steroids for long-term use."

ANTIPHOSPHOLIPID SYNDROME

Savino Sciascia, University of Turin, Italy, discussed the complex pathogenesis of antiphospholipid syndrome (APS), explaining that different mechanisms might justify the heterogeneity of the clinical presentation and the importance of individualised treatment. Maria Tektonidou, National and Kapodistrian University of Athens, Greece, presented the anticoagulant therapy of antiphospholipid syndrome. They discussed the EULAR and ACR guidelines, and presented evidence that direct oral anticoagulants are less effective than warfarin in the treatment of thrombotic APS. Tektonidou also presented evidence that hydroxychloroquine and statins may be considered as adjunctive to antithrombotic treatment for anticoagulant refractory thrombotic APS. Hydroxychloroquine can be considered in patients with recurrent pregnancy complications, despite low dose aspirin and prophylactic low-dose heparin. Doruk Erkan, Hospital for Special Surgery, New York, USA, discussed the presentation and treatment of microvascular and catastrophic APS.

LARGE VESSEL VASCULITIS

Carlo Salvarani, University of Modena and Reggio Emilia, Italy, discussed the impact of age on giant cell arthritis (GCA), immunosenescence and GCA, imaging in large vessel vasculitis, and what is new in GCA therapy. They concluded that tocilizumab can be used in all patients with newly-diagnosed or relapsing GCA due to its efficacy and steroid-sparing effect. However, 1 year of tocilizumab induces prolonged drug-free remission in only half of the patients. Dose reduction or increase of the treatment interval in patients in remission after 12 months of tocilizumab maintained most patients in remission. Secukinumab and mavrilumab seem to be effective therapies in GCA. JAK inhibitors could be effective in GCA, but their use in GCA will be limited by the European Medicines Agency (EMA) recommendations regarding their safety.

PSORIATIC ARTHRITIS

Laure Gossec, Pitié-Salpêtrière Hospital, Paris, France, presented the treatment of psoriatic arthritis. They presented the limited role of non-steroidal anti-inflammatory drugs, the role of conventional synthetic DMARDS, the role of biologic DMARDs, and targeted synthetic DMARDs. Gossec presented the different risks of specific infections with different biologic and targeted synthetic DMARDs. They stressed the importance of different features of psoriatic arthritis, and safety considerations in the selection of the most appropriate therapy.

BEHÇET'S DISEASE

Gulen Hatemi, Istanbul University, Türkiye, discussed the clinical domains, the classification criteria, imaging for the diagnosis of eye involvement, and the effectiveness of different therapeutic agents for different clinical manifestations of the disease. They reported the following changes in the treatment of Behçet's syndrome: apremilast may be used in patients

with oral and genital ulcers, with inadequate response to colchicine; first-line use of TNF inhibitors is increasingly used in patients with uveitis; TNF inhibitors may be used for induction treatment in patients with arterial aneurysms and major venous thrombosis; and TNF inhibitors may be a better option than azathioprine for maintenance treatment of vascular involvement, nervous system, and gastrointestinal involvement.

OSTEOPOROSIS

Natasha Appelman-Dijkstra, Leiden University Medical Centre, the Netherlands, suggested to also do a vertebral fracture assessment during a dual-energy X-ray absorptiometry scan. They advised, if possible, to start anabolic therapy in severe osteoporosis with vertebral fractures. Treating a hip fracture with zoledronic acid reduced morbidity, and decreased the treatment gap after a hip fracture. Appelman-Dijkstra advised to always prescribe follow-up therapy after romosozumab, teriparatide, and denosumab. They recommended to start patients on preventive therapy when starting glucocorticoids.

GOUT

Abhishek Abhishek, University of Nottingham, UK, reported that gout has a strong genetic risk. Lifestyle changes could improve the inherited risk of gout. Some patients may be less responsive to allopurinol due to genetic factors. They suggested to screen for the *HLAB5801* allele in Han Chinese, Thai, Korean, and African American populations (7–8% prevalence) before allopurinol is prescribed, since they are at higher risk of hypersensitivity reaction.

Fernando Perez-Ruiz, Cruces University Hospital, Barakaldo, Spain, presented the challenge in managing gout in patients with kidney disease. Patients with advanced chronic kidney disease are difficult to treat, and high-risk medicines and pharmacokinetic interactions should be avoided. Most urate lowering therapies are safe in renal transplant patients and haemodialysis is effective.

Pascal Richette, Hôpital Lariboisière, Paris, France, gave a presentation comparing guidelines on gout management. They referred to the EULAR, ACR, British Society for Rheumatology (BSR), National Institute for Health and Care Excellence (NICE), and other guidelines. Richette mentioned the significance of lifestyle modification, cessation of hyperuricaemia-inducing drugs, and the role of diet and exercise. They discussed the importance of treat-to-target, the use of urate lowering therapies, the treatment of flares, the use of prophylaxis, and the treatment of comorbidities.

Robert Keenan, Duke University School of Medicine, Durham, North Carolina, USA, presented a 12-week Phase IIb study of AR882 in patients with gout. The majority of patients achieved serum urate levels below 5 or 4 mg/dL, 75 mg AR882 reduced tophi faster than standard oral therapy, and the medication was well-tolerated and easy to use.

WHAT IS NEW ON ULTRASOUND IN RHEUMATIC AND MUSCULOSKELETAL DISEASES?

Peter Mandl, Medical University of Vienna, Austria, gave an overview on the use of ultrasound in rheumatic and musculoskeletal diseases (RMD). They concluded that ultrasound scan is a tool that can provide information in virtually every RMD; it can be utilised in predicting the development of persistent arthritis in patients at risk of developing RA; it is sensitive to change, and may help identify sub-phenotypes in psoriatic arthritis; it is reliable in assessing inflammation in hand OA; it is the imaging method of choice in patients with suspected GCA; and ultrasound scan signs of crystal deposits have high specificity and sensitivity in diagnosing gout.

THE CONUNDRUM OF DIAGNOSING AXIAL SPONDYLOARTHRITIS RESOLVED

Robert Landewe, Amsterdam University Medical Centers, the Netherlands, presented the ASAS Axial Spondyloarthritis Criteria in a historic perspective. Walter Maksymowych, University of Alberta, Edmonton, Canada, presented the CLASSIC study. The rationale was to re-evaluate the 2009 ASAS classification criteria for axial spondyloarthritis.

The primary outcome was to validate the existing criteria with a pre-specified specificity of more than 90% and sensitivity of more than 75%. The CLASSIC study revealed that the sensitivity was 73.8% and the specificity 84.3%; therefore, the primary outcome was not met. They proposed the following steps: discussion and definitions of spondyloarthritis variables, discussions of pros and cons of modifications to ASAS 2009 criteria, and voting of members on preference for modifications to the ASAS criteria.

EULAR RECOMMENDATIONS

Bruno Fautrel, Sorbonne University, Paris, France, and Fabrizio De Benedetti, Banbino Gesù Children's Hospital, Rome, Italy, presented the EULAR/Paediatric Rheumatology European Society (PRES) recommendation for the diagnosis and management of systemic juvenile idiopathic arthritis and adult-onset Still's disease. Gossec presented the 2023 update of the EULAR recommendations for the management of psoriatic arthritis. Boumpas presented the 2023 EULAR recommendations for the management of systemic lupus erythematosus.

CLINICAL/BASIC/ TRANSLATIONAL HIGHLIGHTS

Christian Dejaco, Medical University of Graz, Austria, presented the clinical highlights of the congress. Leonie Taams, King's College London, UK, presented the basic and translational science highlights. These presentations provided an overview of the most important research presented in this year's congress. EULAR 2023 was a successful and enjoyable meeting, and we look forward to the EULAR 2024 congress in Vienna, Austria.

Abstract Reviews

Sharing results of the latest research in rheumatology, from novel abstracts presented at the European Alliance of Associations for Rheumatology (EULAR) Congress 2023.

Predictors of Renal Flares in Systemic Lupus Erythematosus

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Keywords: Biomarkers, lupus nephritis, monoclonal antibodies, systemic lupus erythematosus (SLE).

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BACKGROUND AND AIMS

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a highly heterogenous clinical presentation that can affect almost any organ system.[1] In patients with SLE, kidney disease is one of the most serious manifestations, as kidney failure may lead patients to require dialysis or a kidney transplant.[2] Therefore, identification of patients at risk of developing renal flares despite immunosuppressant therapy is imperative to optimise management and improve outcomes.

In this study, the authors aimed to identify predictors of renal flares in patients receiving treatment for active extra-renal SLE.

MATERIALS AND METHODS

The authors analysed data from four randomised clinical trials of belimumab: BLISS-52,[3] BLISS-76,[4] BLISS Northeast Asia,[5] and BLISS-SC.[6] The trials included patients with SLE who had an active disease despite receiving standard therapy. In this population, the authors investigated several biomarkers that are routinely used in clinical practice as potential predictors of renal flares within 76 weeks.

RESULTS

Of the 3,225 patients enrolled in the clinical trials, 192 developed a renal flare. The factors that were more strongly associated with the development of renal flares were a history of renal involvement (hazard ratio [HR]: 9.4; 95% confidence interval [CI]: 5.0–17.7), baseline serum albumin (HR: 0.9; 95% CI: 0.9–0.9), levels of proteinuria (HR: 1.3; 95% CI: 1.2–1.4), and low complement component 3 levels (HR: 1.8; 95% CI: 1.3–2.5). All these factors predicted renal flares regardless of the treatment that patients received during the clinical trials.

However, the ability of some biomarkers to predict renal flares differed according to the treatment received by the patients, as positive levels of anti-Smith antibodies were associated with renal flares in the placebo (adjusted HR: 2.9; 95% CI: 1.5–5.6) but not in the belimumab

subgroup. Anti-ribosomal P protein antibodies were associated with renal flare development only in patients treated with belimumab (HR: 2.8; 95% CI: 1.5–5.0).

CONCLUSION

In conclusion, the authors identified several biomarkers in blood and urine that are already accessible in the clinic, and may be useful tools to predict renal flares. While some of these biomarkers have an established role in disease monitoring, anti-Smith and anti-ribosomal P protein antibodies constitute novel and appealing candidates. ●

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Work Participation and the COVID-19 Pandemic: A Study Within the Amsterdam COVID-19 Cohort Among People with Inflammatory Rheumatic Diseases and Population Controls

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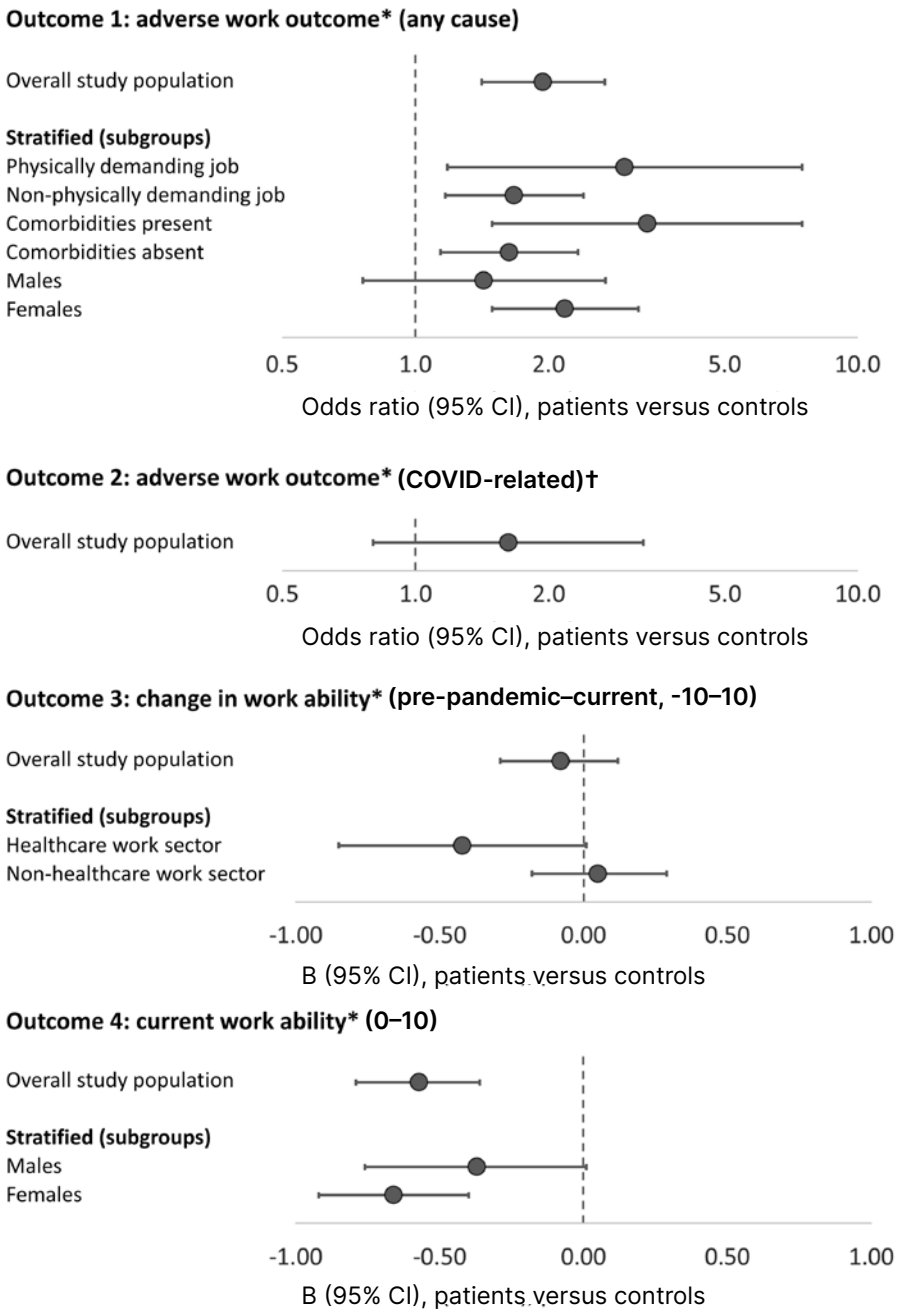
Keywords: Cohort study, COVID-19, rheumatic disease, work ability, work participation.

Citation: EMJ Rheumatol. 2023;10[1]:34-36. DOI/10.33590/emjrheumatol/10309331. https://doi.org/10.33590/emjrheumatol/10309331

BACKGROUND

Past research has repeatedly shown that patients with inflammatory rheumatic disease (IRD) experience restrictions in work participation. Times of crisis tend to bring out such vulnerabilities. The global COVID-19 pandemic is a prime example, and this event possibly widened the work participation gap between patients with IRD and the general population. On the other hand, some of the consequences of the pandemic, such as an increase in working from home, might also provide benefits for patients with IRD.

Figure 1: Association between group (patients versus controls) and adverse work outcome or (change in) work ability in multivariable regression analysis.



*Covariables explored in models (retained if confounder for group and outcome, or if significantly associated with outcome): **age (outcomes 1 and 2)**, gender, education, **comorbidities (outcome 4)**, past COVID-19 infection, COVID-19 vaccination, work sector, job demands, **type of employment (outcome 2)**, **working hours (outcomes 3 and 4)**, **work location (outcome 4)**. Covariables marked in bold if significant.

†Defined as adverse work outcome attributed by the patient to either impact of COVID-19 on personal health or impact of national pandemic measures against COVID-19.

An odds ratio >1 or B <0 indicates a worse outcome in patients compared with controls (higher likelihood of adverse work outcome, a greater decrease in work ability, or lower current work ability).

B: regression coefficient; CI: confidence interval.

MATERIALS AND METHODS

Researchers from Maastricht, the Netherlands, aimed to compare several work participation outcomes during the COVID-19 pandemic between patients with IRD and population controls. A cross-sectional study was carried out within an ongoing Dutch, prospective COVID-19 cohort of patients with IRD and matched controls. In March 2022, participants provided information about their work outcomes and work characteristics in 2022 ('current') and in 2020 ('pre-pandemic', retrospective).

Two work outcomes were considered: adverse work outcome and work ability. Adverse work outcome was defined as any of the following in the 2020–2022 period: withdrawal from paid work, working hours reduction, or long-term sick leave. Work ability was rated on a scale of 0–10 (worst–best), and both current work ability in 2022 and the change during the pandemic from 2020–2022 were considered. These work outcomes were compared between patients and controls in multivariable logistic and linear regression analysis, respectively. In addition, stratified analyses were conducted to identify vulnerable groups. Finally, participants were asked to rate the influence of four typical remote work characteristics (care for children, absence of colleagues, employer support such as a desk or chair, reduced work commute) on their work performance while working at home.

RESULTS

In total, 992 patients and 443 controls were working pre-pandemic. From these, 227 patients (23%) and 79 controls (18%) experienced any-cause adverse work outcomes following pandemic onset (p=0.04). Both patients and controls attributed only 15% of these events to COVID-19 (personal COVID-19 illness or national pandemic measures).

In adjusted analyses, patients were more likely to experience any-cause adverse work outcomes, with odds ratios (OR) ranging from 1.6–3.3 for patients versus controls in various stratified analyses, but not COVID-related adverse work outcomes (Figure 1). Female patients (OR: 2.2), patients with comorbidities (OR: 3.3), and patients with physically demanding jobs (OR: 3.0) were particularly vulnerable for any-cause adverse work outcomes. While the change in work ability during the pandemic was small and very similar in groups, current work ability in 2022 was worse in female patients compared with controls. Of note, a history of COVID-19 was not associated with any of the work outcomes.

When working from home, care for children and absence of colleagues had varying effects on work performance (positive 19% and 24%, respectively; negative 34% and 57%, respectively), while employer support and reduced commuting had mainly positive effects (83% and 86%). These results were similar in patients and controls.

CONCLUSION

This study demonstrates that the work participation gap between patients with IRD and the general population persists. However, there was no clear indication that the gap increased due to the pandemic: patients did not have more COVID-related adverse work outcomes or a greater loss in work ability during the pandemic. Furthermore, although the observation that patients with a history of COVID-19 do not have worse work outcomes is reassuring, the long-term effects of past infection on work participation need further study.

Prevalence of Risk for Anxiety and Depression in Patients with Rheumatic Diseases

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Keywords: Anxiety, depression, mental health, rheumatic diseases.

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BACKGROUND AND AIMS

There is a higher prevalence of anxiety and depression in patients with chronic diseases. In a complex relationship, chronic diseases and mental health disorders can influence each other negatively.[1] Studies have shown that almost one-third of patients with rheumatoid arthritis present symptoms of major depressive disorder or dysthymia, being more prevalent when compared with the general population.[2]

This study aimed to determine anxiety and depression symptom prevalence in an outpatient rheumatology clinic, and its associated factors.

MATERIALS AND METHODS

The authors conducted a cross-sectional study that included patients aged over 16 years old with a rheumatologic diagnosis. Data from the patients' medical history were collected. The Hospital Anxiety and Depression Scale (HADS) was applied from March–November 2022, where a score of 0–7 points was classified as low risk, 8–10 as intermediate risk, and more than 11 points as high risk. Patients at high risk were referred to an evaluation in the psychiatry department in the same clinic. The researchers compared groups according to HADS scores using the Kruskal–Wallis or χ^2 test. A total of 705 patients were involved, including 658 females. The demographic characteristics are outlined in Table 1.

RESULTS

The most common diagnosis was rheumatoid arthritis, followed by systemic lupus erythematosus. High anxiety risk was found in 125 patients with a median disease duration of 10 years. An intermediate risk of depression was identified in 15 patients with a median disease duration of 10 years. The authors found 38 patients who were accepted to be referred for a psychiatric evaluation. An association was found between a high risk of anxiety and gender (p=0.019); however, there was no association with age nor menopause. A high risk of anxiety was more prevalent (n=125) than depression (n=16), and patients with an intermediate risk for depression showed a higher prevalence of intermediate and high risk for anxiety (p=0.000). Almost one in every five patients with rheumatic diseases had an intermediate risk for anxiety.

CONCLUSION

The authors found that a high risk of anxiety was more prevalent than depression, and a higher risk of anxiety was found in female patients. Therefore, constant mental health screening can help patients receive earlier attention by a specialist. ●

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Table 1: Demographic, clinical, and rheumatic disease characteristics.

	Characteristics	HADS A low (N= 77)	HADS A inter (N=103)	HADS A high (N=125)	p	HADS D low (N=674)	HADS D inter (N=15)	HADS D high (N=16)	p
Demographic	Median age, years (iQR)	51.0 (42.5–61.0)	51.0 (45.0–61.0)	56.0 (45.0–64.0)	NS	52.0 (43.0–61.0)	60.0 (38.0–63.0)	59.5 (40.5–69.0)	NS
	Females, n (%)	437 (91.6)	98 (95.1)	123 (98.4)	0.019	628 (93.1)	98 (100.0)	15 (93.7)	NS
Clinical profile	Mean disease duration, years	5.0 (1.00–10.00)	4.0 (1.00–10.00)	6.0 (2.25–12.00)	NS	5.0 (1.00–10.00)	10.0 (1.00–20.00)	10.0 (4.25–20.00)	NS
	Median age of diagnosis, years (iQR)	45.0 (32.0–53.5)	45.9 (35.0–54.0)	48.0 (37.0–56.7)	NS	45.0 (33.5–54.0)	45.0 (31.0–59.0)	47.0 (28.3–58.5)	NS
	Median number of comorbidities (iQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	NS	0.0 (0.0–1.0)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	NS
Rheumatic disease	RA, n (%)	249 (52.2)	52 (50.4)	53 (42.4)	NS	341 (50.5)	6 (40.0)	7 (43.7)	NS
	SLE, n (%)	67 (14.0)	12 (11.6)	15 (12.0)	NS	89 (13.2)	1 (6.6)	4 (25.0)	NS
	FM, n (%)	14 (2.9)	2 (1.9)	3 (2.4)	NS	18 (2.6)	1 (6.6)	0 (0.0)	NS
	SS, n (%)	10 (2.0)	4 (3.8)	5 (4.0)	NS	18 (2.6)	1 (6.6)	0 (0.0)	NS
	SSc/scleroderma, n (%)	10 (2.0)	2 (1.9)	1 (0.8)	NS	12 (1.7)	1 (6.6)	0 (0.0)	NS
	OP, n (%)	15 (3.1)	2 (1.9)	7 (5.6)	NS	22 (3.2)	1 (6.6)	1 (6.2)	NS
	Overlap, n (%)	31 (6.4)	10 (9.7)	21 (16.8)	NS	57 (8.4)	3 (20.0)	2 (12.5)	NS
	Other, n (%)	81 (16.9)	19 (18.4)	19 (15.2)	NS	116 (17.2)	1 (6.6)	2 (12.5)	NS

A: anxiety; D: depression; FM: fibromyalgia; HADS: Hospital Anxiety and Depression Scale; iQR: interquartile range; NS: not significant; OP: osteopenia; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; SS: Sjögren's syndrome.

Abstract Highlights

The following selected highlights spotlight several interesting and timely abstracts presented at the European Alliance of Associations for Rheumatology (EULAR) Congress 2023, covering topics such as recurring joint inflammation in juvenile idiopathic arthritis, systemic lupus erythematosus, and the importance of a healthy lifestyle in patients with osteoarthritis.

Citation: EMJ Rheumatol. 2023;10[1]:39-43.
DOI/10.33590/emjrheumatol/10308364.
https://doi.org/10.33590/emjrheumatol/10308364.

Osteoarthritis: Association Between Healthy Lifestyles and Mortality

OSTEOARTHRITIS (OA), the most common form of arthritis worldwide, affects 527.8 million people. Previous studies have linked OA to higher rates of mortality, compared to the general population. While OA may not directly cause mortality, lifestyle factors such as obesity, low walking frequency, depression, anxiety, unrefreshed sleep, and physical inactivity may be contributing factors to the high rates of mortality. Therefore, a research team at the Southern Medical University, Guangzhou, China, aimed to explore the associations of both individual and combined healthy lifestyle factors with the risk of mortality among patients with OA.

Data from the UK biobank was used to identify 104,142 participants with OA aged between 40–69 years, with follow-up conducted over 10 years. Outcomes measured were all-cause mortality and cause-specific mortality. A healthy lifestyle score was allocated to participants based on physical activity, healthy diet, moderate alcohol, no current smoking, healthy BMI, being less sedentary, social connection, and enough sleep. Statistical analysis utilised a restricted cubic spline fitted for Cox regression models, with a two-sided $p<0.05$ considered statistically significant.

Results showed that the mean age of participants was 59.84 years and 42% of participants were male. The optimal range of lifestyle factors were found to be a BMI between 26–30, sleep duration between 7–8 hours per day, moderate physical activity of over 550 minutes per week, vigorous physical activity of 100–500 minutes per week, and less than 5 hours a day of sedentary time. By using the multivariable Cox regression analysis model, the research team found that each lifestyle factor was associated with a reduced risk of all-cause mortality (hazard ratio [HR]: 0.29), cancer-cause mortality (HR: 0.40), and cardiovascular disease-cause mortality (HR: 0.22) in patients with OA.

"Data from the UK biobank was used to identify 104,142 participants with osteoarthritis aged between 40–69 years."

In conclusion, this study found non-linear associations between lifestyle factors and all-cause mortality in patients with OA, and defined the optimal range of healthy lifestyle factors. This healthy lifestyle pattern could significantly reduce the risk of mortality in patients with OA.

Higher Comorbidity Burden in Early Psoriatic Arthritis Compared to Early Rheumatoid Arthritis

SEVERAL factors contribute to the progression from psoriasis to psoriatic arthritis (PsA), including mechanical inflammation and dysbiosis. Nevertheless, there is limited data regarding the role of cardiovascular risk factors and comorbidities in this progression. While it is known that increased BMI and obesity are risk factors for the transition from psoriasis to PsA, the role of other cardiovascular risk factors and other specific comorbidities in the progression remains unclear.

Alla Ishchenko, Department of Rheumatology, University Hospitals Leuven, Belgium, who presented the data at EULAR 2023, hypothesised that comorbidities (cardiovascular and metabolic) are present at the early stages of PsA, are not only a consequence of long-lasting inflammation, and may serve as a second hit.

Ishchenko and colleagues aimed to investigate the comorbidities associated with metabolic burden and cardiovascular morbidity in patients with early PsA. They compared the rate of comorbidities in this group with that of healthy volunteers matched by sex and age, as well as patients with early rheumatoid arthritis (RA). The study included patients with PsA (n=67), early RA (n=50), and healthy volunteers (n=61). All three patient groups had comparable age.

Numerically, the rate of overall comorbidities was higher in patients with PsA (74%) and RA (67%); however, the difference did not reach statistical significance as compared with the control group. Notably, both patients with early PsA and early RA demonstrated a higher prevalence of multiple cardiovascular risk factors.

Dyslipidaemia was the most prevalent comorbidity in early RA and early PsA. Out of all lipids, only the levels of high-density lipoprotein were significantly lower in patients with PsA. Both patients with PsA and RA had high rates of obesity, whereas this was observed in only one-third of the control group. Both patients with RA and PsA had a higher incidence of Type 2 diabetes, while patients with early PsA had a notably higher rate of depression compared to patients with RA and the control group. The incidence of other comorbidities, including arterial hypertension, gout, malignancy, and all other conditions, was comparable among the three groups.

"Both patients with early PsA and early RA demonstrated a higher prevalence of multiple cardiovascular risk factors."

Despite having similar age and BMI, patients with PsA exhibited a higher prevalence of cardiovascular disease. Moreover, a greater proportion of patients with early PsA had a Charlson comorbidity index of at least 1 when compared with patients with early RA and the control group.

Ishchenko and team concluded that during the early stages of both RA and PsA, patients experience a significant cardiovascular burden. Notably, in the early disease phase of PsA, individuals already exhibit multiple cardiovascular risk factors and comorbidities. Dyslipidaemia and abdominal obesity emerged as the most prevalent comorbidities in this context, highlighting the presence of cardiovascular and metabolic comorbidities during the early stages of PsA.

Recurring Joint Inflammation in Juvenile Idiopathic Arthritis

JOINT inflammation tends to recur in the same joints in patients with juvenile idiopathic arthritis (JIA), according to research presented at EULAR 2023.

JIA is often a relapsing/remitting disease, but the mechanisms behind it and how to prevent it are currently unknown. Sascha L. Heckert, Leiden University Medical Centre, the Netherlands, and colleagues, investigated joint inflammation patterns over time to gain insight into disease flares.

The investigation used data from the BeSt Kids study (N=91), which included patients with oligo-articular, rheumatoid factor-negative polyarticular, and psoriatic JIA. The patients were randomised into three treatment strategy arms. However, if the disease was active, treatment was intensified.

The follow-up was 2 years, with 10 visits. A total of 6,097 joints were assessed for clinical inflammation during this time.

At baseline, 15% of joints were clinically inflamed. Of these joints, a total of 42% flared during follow-up, as opposed to 11% of the joints that were not active at baseline.

The researchers also noted that joint activity at baseline was predictive for activity in the same joint during follow-up (odds ratio [OR]: 3.9; 95% confidence interval [CI]: 3.5–4.3). Furthermore, joints that were inflamed at baseline were 1.6 times more likely to be inflamed during follow-up than those that were not (95% CI: 1.3–2.1).

"A total of 6,097 joints were assessed for clinical inflammation."

Although the distribution of joint inflammation was different in the different types of JIA, the association between baseline and later joint activity was seen in oligo-articular (OR: 3.4; 95% CI: 2.1–5.6), rheumatoid factor-negative polyarticular (OR: 4.1; 95% CI: 3.6–4.6) and psoriatic (OR: 1.7; 95% CI: 1.2–2.7) JIA.

To conclude, Heckert stated that joint inflammation tends to recur in the same joints, which points towards a local effect. While this effect is currently unknown, Heckert believes that this could be due to tissue priming, meaning the tissue becomes susceptible to inflammation once inflamed, and this could be a potential treatment target. ●

Outcomes of Systemic Lupus Erythematosus and Associated Pulmonary Arterial Hypertension Study

THE LATEST results of a 10-year multicentre cohort study on improvements and challenges in systemic lupus erythematosus (SLE)-associated pulmonary arterial hypertension (PAH), a frequent complication of connective tissue diseases, were presented at EULAR 2023. The study's aims were to explore changes in disease characteristics, initial treatment regimen, and long-term survival for patients with SLE-PAH, and to investigate reasoning for improvements in survival.

The study was carried out by the Chinese SLE Treatment and Research Group, using patients found on the nationwide CSTA Registry, including over 100 rheumatology centres across China. It identified 720 patients diagnosed with SLE; 636 of these had SLE and confirmed pre-capillary PAH, and 610 were included in the study. This group was split into two cohorts according to the dates of their diagnosis: A, 2011–mid-2016 (n=314), and B, mid-2016–2021 (n=296). Patients with other comorbidities that cause pulmonary hypertension, including severe lung diseases, pulmonary embolisms, and heart failure, were excluded from the study. Another single-centre cohort of patients with idiopathic PAH was recruited as a control group.

SLE-PAH showed more favourable prognosis than systemic sclerosis-PAH, and a less severe disease condition when compared with idiopathic PAH. Those in Cohort B demonstrated an earlier stage of PAH than Cohort A. Cohort B were also diagnosed later; had lower pulmonary artery pressure, less right heart dilation, and lower pulmonary respiratory resistance; and demonstrated better performance during a 6-minute walk test. More patients in Cohort B were classified into the low-risk group (approximately 47%); treated with PAH target medication (90%); and achieved PAH treatment goals (around 83%).

The 5-year survival rate of SLE-PAH was raised significantly from 73% to 83%, with improvements mostly in those of low to intermediate risk. Rates did not improve in the high-risk group.

Researcher Xingbei Dong, Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, China, stated that whilst the "good news is, during the past 20 years, many PAH-targeted drugs have been developed, and the treatment strategy is constantly being refined," challenges still remain in managing SLE-PAH, and further research is required.

"The study's aims were to explore changes in disease characteristics, initial treatment regimen, and long-term survival for patients with SLE-PAH."

SLE: Diagnosis Ambiguity and Recommendations for the Future

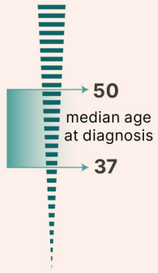
Citation: EMJ Rheumatol. 2023;10[1]: DOI/10.33590/emjrheumatol/10300882. https://doi.org/10.33590/emjrheumatol/10300882

Epidemiology

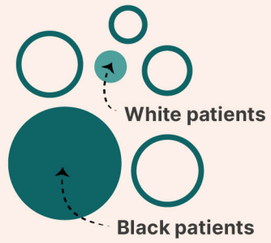
Estimate of the global prevalence of SLE

Tropical Latin America reports the highest prevalence[1]

per 100,00 people (more common in females)



Onset of symptoms usually during childbearing years



Highest and lowest incidence rate in population groups[2]

Clinical Manifestations

90%

of patients display constitutional symptoms such as fatigue, fever, and anorexia[3]

Mild to severe

life-threatening disease with multiorgan involvement

50%

of patients will have kidney diseases during the course of the illness[3]

Over 80%

of patients suffer from mucocutaneous involvement, including ACLE, the hallmark of which is the butterfly rash[3]

80–90%

of patients have musculoskeletal involvement, ranging from mild arthralgias to deforming arthritis[3]

Key

ACLE: acute cutaneous lupus erythematosus; SLE: systemic lupus erythematosus; PCP: primary care physicians.

The Implications of Lupus Diagnosis Ambiguity and Recommendations for the Future

27–37% of diagnoses within 1 year of symptoms[4]

Non-specialists often have difficulty interpreting non-specific symptoms of potential SLE[4]

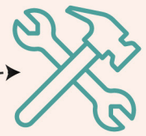
Only 20% of patients recall any mention of lupus from PCP at the first visit[5]

Reduce diagnostic delay so that targeted therapies can be initiated early, reducing long term damage[4]

Adopting a spectrum definition of lupus could help address diagnosis-related challenges[4]

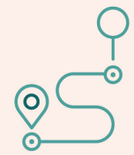
Diagnosis relies heavily on the adaptation of SLE classification criteria, clinical judgement, and probabilistic diagnostic reasoning[4]

Next steps in improving diagnosis:



Implement provider training and provide tools to improve patient care

Send alerts and resources on the latest developments



Develop a clear pathway for referral from PCP to specialist[4]

Leverage emerging research and work with global regulatory health agencies to expand the definition of lupus[4]

Conduct prevention trials to understand whether biomarkers can contribute to earlier diagnosis[4]

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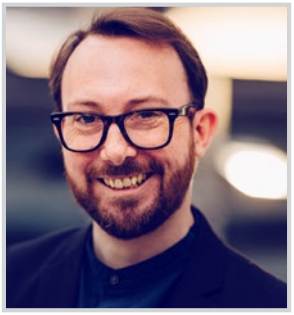
EMJ

Interviews

Chris Wincup, Denis Poddubnyy, Christine Peoples, and Thomas Huizinga spoke with EMJ, sharing details about their careers and research focuses. The experts also discussed a range of field specific topics, including systemic lupus erythematosus, spondyloarthritis, and the value of telemedicine.

Featuring: Chris Wincup, Dennis Poddubnyy, Christine Peoples, and Thomas Huizinga



Chris Wincup

Consultant Rheumatologist, Lupus Unit, King's College Hospital, London, UK; Versus Arthritis Research Fellow, University College London (UCL), London, UK

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Q1 What led you to pursue a career in rheumatology specifically focusing on systemic lupus erythematosus?

I think that I was slightly unusual in my career choices, in that I left medical school knowing exactly what I wanted to do. I went into medical school interested in sports, exercise, and musculoskeletal health, mainly because I was frustrated footballer, who was never going to make it playing at a professional level. But thought that I would like to work in the field of musculoskeletal health, particularly in relation to sport injuries.

During my elective at medical school, I gain experience doing orthopaedics, and I realised that I was not cut out for that. I recall being told that my history taking was overly detailed, but I enjoyed being inquisitive. However, it was at that time that I was introduced to a few patients with rheumatic conditions. The thing that really struck me was how fascinating it was that the patients did not just have problems with their joints, but they also had problems with their lungs, heart, kidneys, eyes, and skin. Something that I was really interested in is that it was not just a disorder of the joints, but it is systemic! I found that really fascinating and that lends itself to my very long and detailed history taking.

So, like that, I was interested in rheumatology! At medical school we had quite a few lectures on lupus, and I really found it absolutely fascinating. It was a disease that was very poorly understood. I remember being told that if you learnt anything about the disease, you are probably breaking new ground. The disease also seemed to be quite discriminatory in the way that it presented; it predominantly affects younger patients and is nine times more common in females than males. Patients also have worse outcomes if non-Caucasian. The disease has

significant impacts on quality of life, in addition to being immunologically fascinating and I think this is what drew me to it.

In my final year of medical school, I decided that I wanted to do lupus, and that I wanted to do a lab-based PhD looking at lupus, Then, 10 years later, that is where it led me, and I have been focusing on lupus ever since. Last year I was appointed as a consultant here at King's College Hospital, London, UK, to focus specifically on lupus.

Q2 As a Lupus UK funded researcher, what research projects are you currently involved in?

I have done lots of different projects in lupus! Being so passionately interested in the subject, I am keen to know about all areas. Some of my research is quite clinical; I am interested in outcomes, but also focusing on what the barriers to good quality care are. We are also currently working on a research project investigating patients' diagnostic journeys. For example, we are asking 'how long does it take to be diagnosed with lupus?', 'What is the impact of being misdiagnosed at the start of a patient's journey have on their future care?', and 'how does this impact on their trust in clinicians and future worries?' That is what led me to develop an interest in mental health and neuropsychiatric lupus.

We know that lupus is a chronic illness that is not curable, has flares, and can be associated with high levels of pain and fatigue, as well as other complications that ultimately have a significant impact on quality of life. We also know that patients suffer with poor mental health. In many cases, we see high levels of anxiety and depression; but we also know that neurological inflammation can occur as a result of the disease, which is poorly understood, and doctors may not be very good at picking that up. We have a major research focus on the neuropsychiatric and mental health manifestations of lupus at the moment and are doing a number of global studies, working with doctors and patients from around the world to get their opinions on when they may worry about these symptoms. This has really informed my clinical practice because when we know that these patients have these symptoms, it then prompts me to ask those questions to better identify them. It gets slightly tricky when patients do admit that they have these mental health symptoms and worrying symptoms such as feeling suicidal or having hallucinations. As a rheumatologist, we are not well trained in what to do once we have identified this. So, we are working on ways to collaborate better with neurologists and psychiatrists to support patients and provide better care.

I am also doing some work in response to lupus therapy, in particular in the role of B cell depletion therapy. We use rituximab quite a lot for severe cases of lupus and I use it often in my practice; however, it does not guarantee a response in every patient. Some of my research into this area is trying to work out why patients may have a good or a poor response to treatment and why some patients have side effects from treatment while others may not. This is so that we can tailor treatment to patients a bit better. As a doctor, we all want to be able to tell patients when we are confident that a treatment will be both effective and well tolerated with confidence.

This leads on to my third main area of research interest, which relates to precision medicine. We are fortunate that, after many years and trials failing in lupus and not having many treatment options, we are starting to see new drugs become available. In 10 years, we will hopefully have even more drugs available, but it will be very difficult for us to know who gets what drug when and for what type of disease. Obviously, we want people to be on the right drug first time rather than go through a trial-and-error process. So, a lot of my laboratory research is now focusing on if we can find markers that allow us to identify if one person will respond very well to a certain treatment, whilst they may not respond to another treatment. This will allow us to personalise care for patients onto drugs that are effective and safe for them.

"We use rituximab quite a lot for severe cases of lupus and I use it often in my practice; however, it does not guarantee a response in every patient."

"One of the other misconceptions is that it is relatively mild illness, where there only mild symptoms like rashes, joint pain, and mouth ulcers."

Q3 What was the main finding of the paper you recently co-authored, entitled 'Anti-rituximab antibodies demonstrate neutralising capacity, associate with lower circulating drug levels and earlier relapse in lupus''?

Rituximab is a drug that depletes the B cells in patients with lupus, which we know is one of the main drivers of many people's lupus. We use it quite a lot here in the UK and I've got quite a lot of experience with it. I was interested that we also use the drug for other conditions, such as rheumatoid arthritis and vasculitis. For patients with lupus, there is risk of infusion reactions, in which they feel unwell when the infusion is being given. Some of these reactions can be more severe in very rare cases, such as full-blown allergic reactions to the treatment. But we do not usually to see that in other conditions that we treat with the drug, so this seems to be a problem only in lupus. We started with a study where anti-drug antibodies had been measured in several lupus patients. I wondered whether these antibodies drove the infusion reactions, and I looked back through the notes, and we published a study showing that if you have these anti-drug antibodies when you undergo retreatment with the drug, you are likely to have one of these reactions. If we knew that routinely in our practice, we may decide to avoid that treatment if we feel people are at sufficient risk of a bad reaction.

I was then interested to see what the effects of these antibodies were over time so I designed a second study where we recruited patients and measured the anti-drug antibody levels shortly after treatment: 6 months, 12 months, and 3 years post-treatment. What we found was that these antibodies persist for a long time. The next question was: 'what does this do to clinical outcomes?' Having shown that it can cause infusion reactions, we questioned if it affects the way the treatment works. What we found was that, if you have the antibodies, you respond well to treatment initially, as well as people who do not have the antibodies. However, patients with anti-rituximab antibodies saw the disease flare much earlier. The positive response to treatment was not as long lasting in patients with the antibodies. Then we took this to the laboratory, and we found the antibodies were capable of neutralising the drug. What we are seeing is a good response to treatment but then the antibodies knockout that response and people flare earlier. So, we now know that these antibodies play an important role in infusion reactions but also in preventing long-term benefit from the treatment. That is important because new drugs that target the same kind of mechanism are becoming available. Therefore, we may want to use those drugs in patients who have the anti-drug antibodies.

Q4 What do you believe are the common misconceptions around lupus?

Lupus is the most common rare disease, affecting approximately one in 1,000 patients, which does not sound all that common, but if you are working in a relatively small general practice surgery in the UK and you have a population of 5,000 people, that is still five people with lupus within that cohort, and four of them may have a diagnosis. But there may be one of those who are not yet diagnosed, and so there are often misconceptions that it is very, very rare. This problem is further compounded as many of the symptoms of lupus cannot be seen physically, which means that the delay in getting diagnosed. This is why lupus is often termed 'an invisible illness'.

One of the other misconceptions is that it is relatively mild illness, where there only mild symptoms like rashes, joint pain, and mouth ulcers. However, they are not mild symptoms for patients, and we know that symptoms like fatigue a very debilitating. It is not a disease to be taken lightly, and I think many people forget that is associated with kidney disease. We know that 50% of people with lupus develop kidney disease, and if that is not recognised, it can severely damage the kidneys, sometimes to the point where people may need dialysis. In a small number of patients that can be life-threatening. I think sometimes people see lupus as this quite benign condition that is very rare. But actually, it is probably more common than people think. It takes a long time to get diagnosed and it

does have very severe manifestations if it is not recognised. I often go around encouraging colleagues to consider that when you've got a patient where the diagnosis is not clear, think of lupus and test for it!

Q5 How important is the early diagnosis of lupus and how can we move towards this?

In the UK, we have an open access healthcare system, where you do not need to pay to see a doctor; you can see a general practitioner and then you can go to hospital and there is no charge. However, the time from the first presentation of lupus symptoms to getting diagnoses is, on average, about 7 years. And that is in a system without any financial constraints to prevent an individual from going to hospital, seeing a doctor, and getting tested. That is probably because the symptoms are very subtle early on and then, as they become more severe and more obvious, it is easier to make a diagnosis. But early diagnosis is important in lupus as the main aim of treatment are to suppress the inflammation in order to control the disease activity. If you do not do that quickly, then you get damage. For example, if you do not pick up kidney disease quickly, and treat it quickly, then the disease will progress; your get more activity in the kidney and that will lead to scarring. When you do eventually recognise it and treat it, you can switch off the inflammation, but if the damage is done and there is scarring, this cannot be reversed. This is why early detection is really important from a clinical point of view.

From a patient's perspective, 7 years is a very long time to be ill without a diagnosis, and that causes a lot of anxiety. Patients will often get a wrong diagnosis before they are being told that they have lupus. So, a patient is often told that they have another condition by a doctor, and then they see me, and I tell them that it is something else. Being diagnosed incorrectly to begin with, and being unwell for so long, can be difficult for patients, and they may struggle to trust doctors again. An earlier diagnosis means that the patient journey is shorter, and they are more confident in the long-term care that they receive. It is all about getting the diagnosis right. But I do appreciate that many doctors are unfamiliar with lupus.

Q6 Across all medical disciplines there is a focus on personalised medicine. Do you believe this will ever be possible for lupus?

I certainly hope it will be! We have had a lot of years where drugs have not worked with lupus and have had to adopt drugs used in other conditions that we think are similar to lupus. We are using the limited number of medicines that we have available to us in the instances when someone is very unwell. But, as new drugs become available, we now have a choice, which is new for lupus. Before we would have perhaps two drugs for someone who is very severely unwell before, but now we have up to perhaps three or four, if the trials are successful. In 10 years, we may have considerably more than that!

As I mentioned with my work in rituximab, we know that this drug works very well for a lot of patients, but some may not tolerate the treatment because of a reaction, or they may not respond to treatment where we had given them medicine that depletes their immune system but not made them better. So, it is absolutely vital that, in the future, we say: "This is what is driving your lupus, and this is the drug that switches that off, and we are very confident that it will work." It is currently not as simple as you have lupus in your kidneys, so this is the treatment that will work for that. I think that we need to find more molecular or tissue markers to give us a clearer idea of what is driving the lupus. A good analogy might be the way we treat cancer. You would not treat it without a biopsy or an idea of what is going on at the cellular level. You can tailor the treatment more appropriately that way, and maybe we need to think in that way with lupus.

Q7 What are the main focuses of your roles in the BILAG Lupus Expert Group and the European League Against Rheumatism (EULAR) Lupus Guidelines Group?

The EULAR Guidelines Group is meeting very soon to update the guidance treating lupus. This is a revision of the guidance from years ago and really does kind of show how much has changed in the lupus landscape and how much we have learnt over a very short period of time. This is because new drugs are becoming available. However, not all drugs are available in every country, and the way that drugs are commissioned and licensed varies from country to country. So, the EULAR task force is looking at Europe and we will look at all the evidence and make broad suggestions on how to treat with the evidence that we have got at the moment. But there will probably be caveat as to what is available locally. I am looking forward to those discussions because I think a lot of people feel drugs work well in different scenarios. I am sure that it will be very educational to participate in.

The BILAG is a group of lupus experts based in the UK and we are updating the UK guidance on the management of lupus. Again, it will be a very big update given that lots of new drugs are available, and it will be more bespoke and tailored to what we do in this country. We are looking at the main healthcare system and the accessibility of various drugs to that system. The group is also working on a number of studies to look at how lupus is diagnosed, what treatments we use, how patients should be monitored, and how we should appraise their disease activity.

Q8 What do you believe are the biggest challenges for clinicians working with patients with lupus and what advice would you give them?

It is important that clinicians think about lupus as a diagnosis. If you are not a doctor who specialises in lupus or a rheumatologist and you have a patient where the diagnosis is unclear or you have tried different treatments and things are not working, it is often useful to consider lupus and referring to a rheumatologist. I think that the number one challenge is to make sure that people are aware of the disease so that they think about referring patients to rheumatologist who then have an easier job of testing for lupus, which is something we are very familiar with. It is very hard for us to diagnose lupus without someone saying, 'could this be lupus?' and then sending the patient to us.

The main challenge for rheumatologists looking after lupus is that the treatment is still imperfect. In some cases, the treatment can be quite toxic and associated with side effects. So, one of the main challenges Is making sure that we have good communication with our patients. If we are going to start them on a medicine that they may get side effects from, we need them to still be confident that when we offer them another medicine, the results will be different. I think that it is really important that we have good relationships with our patients, and that patients feel confident and comfortable in telling us how they feel they are getting on without fear that we will be very paternalistic and tell them they must take their medicine. One of the key challenges is to make sure that we are focused on the patients and how they are tolerating their treatment.

Q9 Are there any exciting innovations on the horizon within the wider rheumatology field?

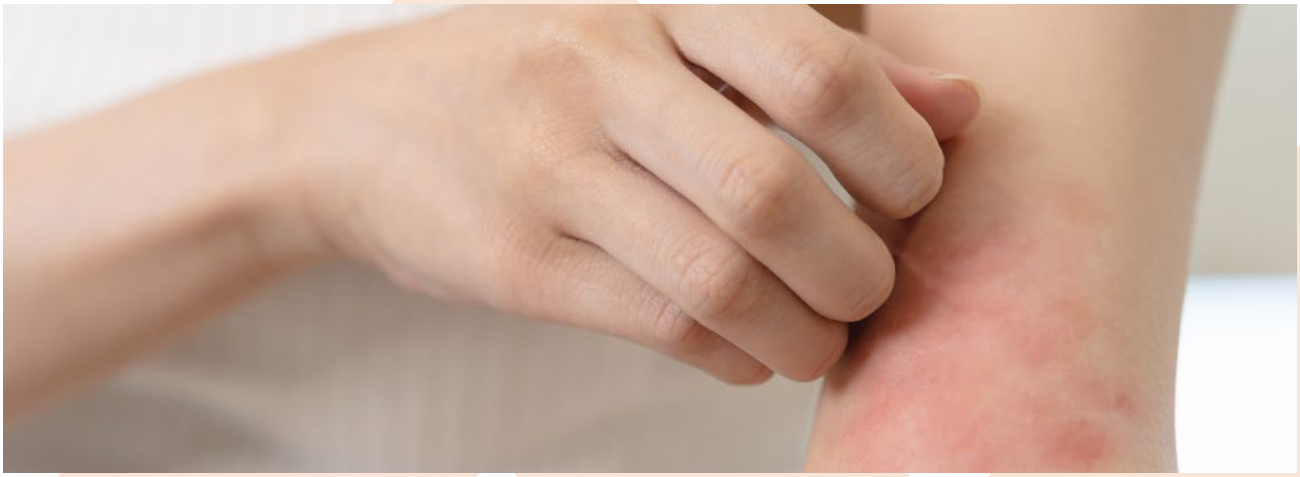
In lupus, as with all of rheumatology, we are now getting a better understanding of how these

diseases occur. As we better identify what is driving the illness immunologically, we are finding better ways of targeting them with therapeutics. As lupus doctors, we often look at our colleagues caring for patients with rheumatoid arthritis enviously, given that there are multiple different drugs that can make rheumatoid arthritis better, especially as there is a lot of knowledge about that disease now. I hope that we will move onto similar horizons in the treatment of lupus soon.

One of the main challenges that we need to think about is if we can catch patients with rheumatic diseases (particularly lupus) earlier in their diagnostic journey. In some cases, by the time patients come to us, they are very unwell with symptoms, and we then confirm the diagnosis. But is there a window of opportunity where the immune system is starting to change towards an autoimmune disease, and that is the point that we may be able to catch them and switch things off before it even starts. In the future, it would be interesting to see whether we can do this.

Q10 There has been talk of moving to a spectrum definition of lupus, do you think this will be beneficial for patients?

I have patients who are close to lupus, where they have some positive antibodies and some symptoms but not enough to give them a diagnosis of lupus. In some cases, they then pick up symptoms or blood tests that, then in a few years, this becomes or confirms lupus. Whereas others will then pick up other symptoms that may develop into another condition such as Sjögren's syndrome or scleroderma, while others will just stay in that group that we call 'undifferentiated'. I often say to the patients do not yet fall into one of those categories or on a spectrum of a lupus-like disease that it does not often impact their care hugely. I would treat that very similarly to the way I would treat lupus based on the symptoms. The only impact it would have on them would be if we were doing a study in lupus where we have to be 100% sure that the meets criteria for lupus. So, it means that they may not be able to go into certain clinical trials. In clinical studies or trials, we have to be completely sure that that person has lupus because we really need to see whether that drug makes it better to be completely sure of it before going into clinical practice. I tell patients to watch out for symptoms, and if they get these extra symptoms (I usually give them a list), then then need to let me know and we may then reclassify things. Ultimately, if they have some joint pain and rash, I may start them on hydroxychloroquine, which is exactly what I would be doing if they had lupus. It is important to have consider that telling patients that they are on a 'spectrum of lupus' that can induce some anxiety, and I do appreciate this. There is actually quite a lot of anxiety in patient groups where we tell them that they had undifferentiated diseases that could progress into something more serious or might actually not progress at all. This is because rather than saying you have lupus and you can read about lupus, we are saying that you may get lupus or you may get these other conditions, which can contribute to anxiety. It is important that you communicate that with patients. I want patients to let me know if their symptoms change because then they may ultimately be moving along the spectrum towards something different. Clinically, a lot of us do think of many autoimmune conditions to be on spectrum already.



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Q1 What do you feel are the current unmet needs in rheumatology, and how could these be addressed in the future?

I think there are several unmet needs in rheumatology, and they might have a higher or lower relevance depending on the field we're working in. For example, I'm working in the field of spondyloarthritis, and there we have unmet needs related to the proper diagnosis of spondyloarthritis. This is related to the fact that the diagnosis is like a puzzle, and there are many puzzle pieces. Whether each piece is correct largely depends on the interpretation of the information, for example, the correct interpretation of imaging findings.

We also have a problem, or an unmet need related to precision medicine. We have plenty of novel drugs, which is especially true for rheumatoid arthritis (RA), psoriatic arthritis (PsA) and to some extent axial spondyloarthritis (axSpA). However, we still do not have clear indicators or parameters to select the right drug for the right patient. Prediction of treatment response in a short and long-term perspective is an important issue for clinical practice.

We also have unmet need in terms of rather rare conditions where we do not have many therapeutic options. I'm referring to some forms of systemic inflammatory disorders such as mixed connective tissue disease, sarcoidosis, and some forms of vasculitis, where we haven't seen any major developments in terms of new treatments or the development of new treatment options in recent years.

Q2 You have a particular focus on spondyloarthritis. What do you feel is currently overlooked in this disease?

In the field of spondyloarthritis, we had a great deal of development over the past 20 years. This is largely related to the invention and implementation of new treatment options used in daily clinical practice, including biological disease-modifying anti-rheumatic drugs (DMARDs) such as anti-TNFs, IL-17 inhibitors, and, lately, taregted synthetic DMARDS such as JAK inhibitors. We could improve the early diagnosis of axSpA. Currently, we can diagnose the disease fairly early, and we face an issue of making the correct diagnosis, especially at the early non-radiographic stage, where there is a substantial risk of misdiagnosis. If the diagnosis is solely based on, for example, the evidence of bone marrow oedema in the sacroiliac joints. However, we have learnt how to differentiate mechanically induced bone marrow oedema from that caused by inflammation, and this is something we try to disseminate currently. So, in our educational activities, we focus on making the correct diagnosis, because an accurate diagnosis is the best predictor of good treatment response.

"The problem, usually in the majority of cases, is that Whipple's disease is recognised very late, because the patient might present with typical rheumatic symptoms such as arthritis."

Q3 In 2021, you co-authored a paper entitled 'Differential diagnostic value of rheumatic symptoms in patients with Whipple's disease'. Could you outline your findings from this paper?

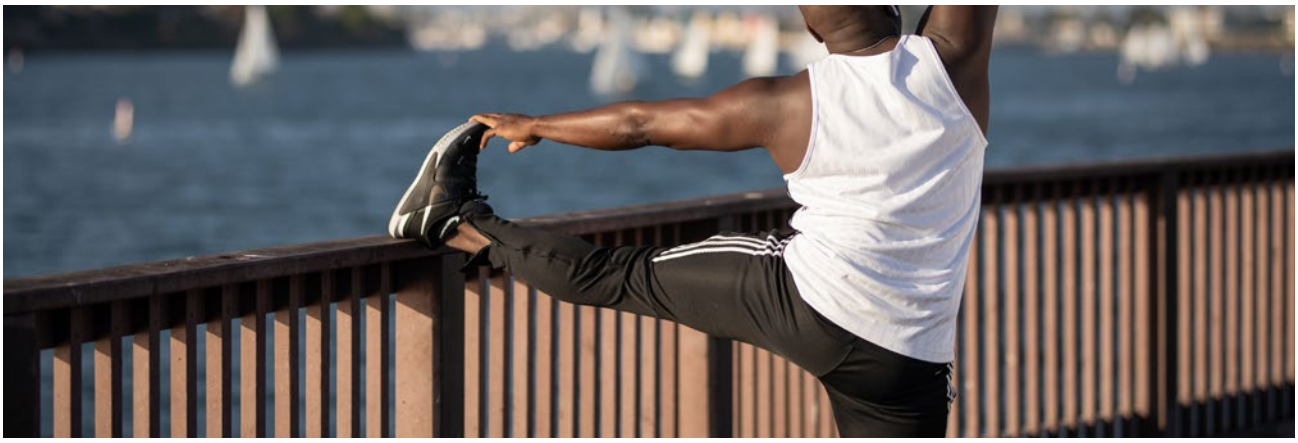
It was very interesting to work with a specialist in infectious diseases. Whipple's disease is a very rare infectious disease, and I was visiting patients in the inpatient department with a specialist in infectious diseases, he asked if I would be happy to contribute to a paper. In this work, we looked at the clinical pattern of symptoms in patients who received the diagnosis of Whipple's disease.

The problem, usually in the majority of cases, is that Whipple's disease is recognised very late, because the patient might present with typical rheumatic symptoms such as arthritis, and normally they are diagnosed with seronegative RA, and treated as such through the application of methotrexate, steroids, and later biological and targeted synthetic DMARDs. After months, or even years of ineffective treatment, there is a realisation that it might be Whipple's disease. So, we tried to find early indicators that there might be a need to look for Whipple's bacteria in the duodenum, for example.

What was quite interesting is that there was a specific pattern of joint involvement, so patients reported a sudden onset of joint pain, with swelling, sometimes going from one joint to another within several days. This presentation of sudden onset pain that changes localisation is not typical symptoms for normal RA. Such a pattern might also be observed in patients with crystal-related arthritis. Once the latter potential cause of symptoms is excluded, there is a possibility that this is Whipple's disease. Thus, Whipple's disease is often associated with specific patterns of joint involvement, which might prompt rheumatologists to look for Whipple's disease.

Q4 You are currently examining whether biomarkers can reflect the structural progression of axSpA, osteoarthritis, and RA. Can you report your current findings, and how you hope this investigation will impact patients?

We started looking for biomarkers as predictors of structural damage progression in patients with axSpA over a decade ago. We learnt that elevated markers of inflammatory activity, such as the C-reactive protein, but also calprotectine and matrix metalloproteinase-3 are a predictor of structural damage progression. We thought that we might be able to find other biomarkers, for example, reflecting new bone formation and bone turnover, which would help us to identify patients at high risk for structural damage progression and that might have relevance for treatment if we are able to delay structural damage progression. So, we looked at many different biomarkers, from acute phase reactants to markers of bone metabolism and adipokines, and we were able to find some predictive and protective biomarkers; however, none of them could be incorporated into daily clinical practice because we have already quite strong predictors of future progression, namely elevated inflammatory activity, already present structural damage, smoking etc. It is difficult to identify biomarkers with added value to these strong predictors. One aspect that was, however, quite interesting in this research was that we identified



that adipokines, such as leptin and high molecular weight adiponectin, were protective against structural damage progression. This is important from a gender perspective, because females have naturally higher levels of leptin and adiponectin, and epidemiological studies have shown that females develop less structural damage in the spine compared to males. Therefore, this might be related to this natural protective high level of leptin and adiponectin.

Q5 Is there any upcoming research you believe will be notable, or perhaps innovative, in the field of rheumatology?

I think that there are several very interesting developments on the horizon in rheumatology, and they are related to different aspects. Firstly, we are seeing really powerful general development of methods of artificial intelligence, including deep learning. So, I would expect to see the development of tools that would support making diagnoses in patients with rheumatic conditions in the next few years. This might be based on the evaluation of symptoms as expressed by a patient, but also the interpretation of imaging findings. I would also expect new imaging methods to improve the diagnosis of rheumatic conditions and the prediction of structural damage development across different conditions.

In terms of treatment, I do hope that we will be getting closer to the use of precision medicine to identify and apply individualised treatment strategies, and I hope that we will be able to interfere with the immune system in a better, more precise way compared to what we're doing now. There are several interesting works focused on the certain inflammatory pathways, which are moving towards the identification of disease-relevant cells, which can potentially be targeted that are directly affected. This would be a next big breakthrough since the development of biological DMARDs.

Q6 You are a member of the executive committee of the Assessment of SpondyloArthritis International Society (ASAS). What are the aims of the society, and how has your experience on the committee been thus far?

ASAS is a group of international experts interested in the field of spondyloarthritis. T his group was largely responsible for the major developments and improvements within the field in the past few decades. This group developed new classification criteria that covered the advanced stage of the disease and the early disease stage. The group developed a number of instruments for the assessment of the disease in clinical practice and research, and was also responsible for the development of international management recommendations based on evidence.

My experience is very, very favourable. I was able to contribute to a number of initiatives within this group, and this refers specifically to the management recommendations, the ASAS core set, and to an initiative related to the development of a consensus definition of axial involvement in PsA. This is an initiative that we conduct with another expert group dealing with PsA, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). Recently, we have started another initiative on the definition of difficult-to-treat or difficult-to-manage spondyloarthritis. We are just at the beginning, so we are planning to find out how to optimally define this clinical situation. Regarding the next steps, I would expect that we will be able to provide recommendations on how to deal with this situation in daily clinical practice and clinical trials.

The group is also working on several very important educational initiatives such as a slide library, which is quite a unique project that contains more than 500 slides covering all aspects of spondyloarthritis in 14 languages and is free to use across the world. Similarly, we started an initiative known as the ASAS case

"We learnt that elevated markers of inflammatory activity, such as the C-reactive protein, is a predictor of structural damage progression."

library a couple of years ago, where we show the entire diagnostic process, starting from patient symptoms, through imaging, to evaluation of the whole picture; here we put imaging into clinical context and educate on the diagnosis and differential diagnosis of spondyloarthritis.

Q7 You are part of the steering committee of GRAPPA, which was set up to allow the sharing of information and research in psoriasis and PsA. In your opinion, what are the biggest achievements of the group so far, and what is GRAPPA hoping to achieve in the future?

GRAPPA is a research group of experts and patient research partners with a special interest in PsA. I'm trying to put effort into working in the interface between PsA and axSpA, and this is how we started the already-mentioned initiative of axial PsA. GRAPPA has been very successful over the past few years in establishing outcome measures and treatment guidelines in PsA. GRAPPA is a platform connecting dermatologists and rheumatologists from all over the world who are interested in the problem of psoriasis and PsA. This is a quite an effective platform that supports the conduction of collaborative projects, related to clinical and basic aspects of PsA.

Q8 You are a Principal Investigator in the AXIS study. Could you tell us what you hope to discover and any findings to date?

AXIS started a few years ago as a small initiative, during which we tried to find an expert consensus definition of the axial involvement in PsA. We very quickly identified that it would be difficult to impossible to test any new definition in the existing patient cohorts, and we realised that we needed to recruit a new cohort of patients with PsA to characterise the axial domain in a standardised way. This is how we came to the prospective part of this study It took a while until we managed to begin this study, because we wanted all study centres to perform standardised imaging examinations of the sacroiliac joints of the spine, including X-rays and MRI. Now, however, the study is ongoing, and we are very happy that we have more than 50 centres from over 20 countries all over the world, including Europe, North and South America, Australia, Africa, and Asia; and the study is recruiting well. We have recruited more than 200 patients; however, we expect to recruit 400 patients in total. We will likely complete recruitment by the end of this year and, afterwards, we plan to analyse the data and to come up with a draft definition of axial PsA. I do believe that, in addition to the definition, we will learn a lot about axial involvement in patients with PsA, and about similarities and differences to primary axSpA.

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Q1 What led you to pursue a career in rheumatology?

There are two main reasons that led me to pursue a career in rheumatology. Growing up, I was a voracious reader (I still am). I loved mysteries such as the Nancy Drew series and all books by Agatha Christie. I knew I wanted to be a doctor from a young age, and so, when I was in college, I started learning about the field of rheumatology. It seemed as though rheumatologists received the medical mysteries to solve. After attending medical school, it seemed like a natural progression to choose rheumatology as my field of study. When we had cases on rounds that no one had a sense of what was going on with the patient or how to interpret certain test results, they called rheumatology. That aspect really drew me to it, and it still does to this day.

The second reason is taking care of patients over time. There are many aspects of long-term care that I enjoy with primary care, but I wanted to specialise. As rheumatologists, we are "super internists", and we do maintain long-term relationships with patients. We must have a strong foundation of all internal medicine concepts. I love that part about it.

Those two reasons are what really drew me to rheumatology, and still pique my interest to this day.

Q2 You are an advocate for telemedicine. How do you see this changing the field of rheumatology in the near future?

I feel telemedicine has already changed the field of rheumatology in many ways, and I think it will continue to change it. In the US, we face a significant shortage of rheumatologists. We need to have ways to provide rheumatology care to those that live in rural areas and to those that cannot access our clinics in the cities for various reasons.

When I started seeing patients through telemedicine, there was a great need in rural and underserved areas of Pennsylvania, along with the surrounding states. Many states in the US are similar, with most rheumatologists clustered in cities. We have examined access issues for patients, and we estimate, in rural and underserved areas of Pennsylvania, that 40–50% percent of patients would just never see a rheumatologist. I could not let that go; patients needed rheumatology care.

Patients are seen at rural telehealth centres, where there are registered nurses that I have personally trained do a comprehensive rheumatological exam. I am on the screen the entire visit, and we talk about everything; there is a great deal of patient "contact" with me, even though I am not physically there. We have worked very hard over the years to optimise a thorough physical exam. Visually, I can see a lot;

"I feel telemedicine has already changed the field of rheumatology in many ways, and I think it will continue to change it."

we have different cameras. We have a Bluetooth stethoscope so I can hear heart and lung sounds. I've been very fortunate to work with the same teams over the past decade at all the telehealth centres. Our teams are committed to provide rheumatology care in this way.

The COVID-19 pandemic was telerheumatology on steroids. Everybody had to be seen remotely, especially when cases were high. Then, that put the focus on: "Hey, wait a second, we need to restructure this, and ensure there's greater access. How can we make it better? How do we get all this organised with patients?" I always love to hear about patient experiences with telemedicine. We obtain surveys about the patient's experience, and how long it took them to block off time from work or manage childcare to come to appointments, because for most folks, it's not a quick appointment. There's a lot to talk about and consider, including their symptoms and treatment options. If they can drive only a short distance to the telehealth centre, or even stay at home, that is a big savings for them. We focus on how we can optimise providing virtual care, as there are different modalities to do so. Telehealth was already changing rheumatology, and, with the COVID-19 pandemic, it has skyrocketed.

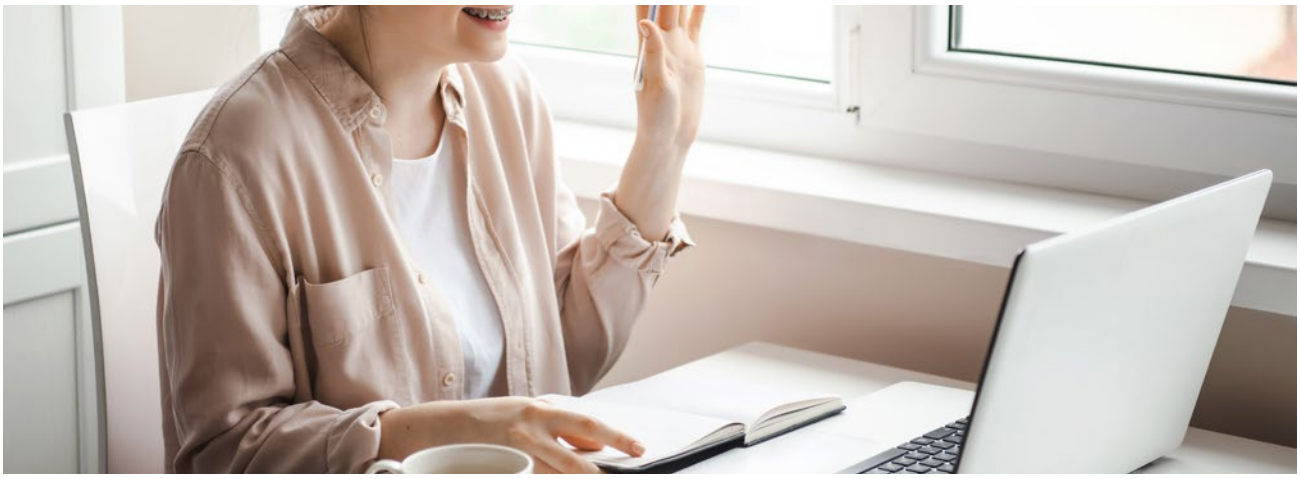
Q3 What does your role as Director of the Rheumatology Telemedicine Program at UPMC involve, and are there any challenges associated with this role?

One of the biggest aspects that I focus on is how to innovate telehealth modalities. We always receive requests about opening new telehealth centres. Are we able to open new locations to service a bigger area of patients? Yes, we can! We were able to hire another rheumatologist to join me last year, and that's been wonderful. We have also hired our own nursing staff for our telehealth patients. We are optimising getting the word out to all the communities we serve.

One of the biggest things that we struggle with, and I think we always will, is medical records. Many patients I see are not within our own UPMC electronic medical record and obtaining outside records remains a challenge. Communication with primary care providers can also be a challenge, as well as managing referrals. There is a significant lack of primary care in rural areas, not just a rheumatology shortage. Currently, we are working on how we can further improve the physical exam. Several of my colleagues specialize in areas like myositis and scleroderma. How can we incorporate their exam pearls into the virtual exam? There is a great deal we can do visually. We are working on revamping some of the nursing training videos, and whether there are other cameras to use with other tools in the physical exam. We can take pictures of a patient's hands and feet, for example, and upload the pictures into the chart. For example, for rheumatoid arthritis patients, we can have standard views that we obtain on each patient.

Q4 What were the main focuses and aims of the 'Telerheumatology' textbook that you edited and authored chapters for?

This was the first work of its kind. The whole concept arose during the COVID-19 pandemic, and that is when I was approached to lead the project. Most people that provided care like this before the pandemic I did not know on a personal level, so I did a great deal of outreach via email. I was fortunate that most people I contacted said they would love to be involved in the project. I was able to network with other rheumatologists, and outline how remote rheumatology care is approached internationally. Since telemedicine is such an umbrella term, it was interesting to see whether we could standardise things, and how we could improve aspects of care for our patients. The book details the fundamentals of providing virtual care in the field of rheumatology. I lead and direct our rheumatology eConsult program. Rheumatology eConsults, which are provider-to-provider consultations, allow us to replace so-called 'curbside consults', where our colleagues in primary care and other specialties ask what they should do with a particular patient with a rheumatology concern. With an eConsult, we have appropriate documentation in the medical record. We review the patient's records and provide recommendations. All telehealth modalities provide a challenge, in that we have choices. You can come to the office for regular visit. You can have a visit from home. You can go a telehealth centre for a visit. You can provide eConsults. What is the best way to make the visit type choice and how can we make this process efficient?



The textbook outlines the breadth of what we do, and leaves the questions: how do we optimise this, and how do we make it easy to select these different visit types? We certainly need more research, and more systematic reviews. The textbook is mainly targeted to rheumatologists and rheumatology trainees. There is a great deal of information that would be relevant to primary care, and for the support staff we work with, such as nurse practitioners, physician assistants, and nurses, that are involved in different telehealth modalities.

Q5 Do you believe there are any misconceptions about the field of rheumatology?

I still think rheumatology is a "black box" for most people. I was the only one in my medical school class that went on to pursue a career in rheumatology, and the only one in my residency class. It's still viewed as very complicated. There are many blood tests, as well as numerous symptoms: how do we evaluate these patients? A lot of people just put up their hands and say they just don't understand rheumatology. It's our job as rheumatologists to help educate our colleagues about certain fundamental concepts in rheumatology. I think gout is an excellent example; it's so common and is becoming more common. There is no way rheumatology can take over the management for all patients with gout, so we need to outline to primary care providers, and other specialists, the basics. This starts at the medical student level in terms of teaching, through residency, and then fellowship. I think getting over that hump is key, instead of "I don't know, just refer." What do they need to know, and when should they suspect something else is wrong, or something rare is happening?

Q6 UPMC is a world-renowned healthcare provider, pioneering ground-breaking research and treatments. What do you think other hospitals could learn from how you operate?

One of the biggest aspects at UPMC is innovation. We had most of our virtual care in place before the COVID-19 pandemic, investing in telehealth centres around 10–15 years beforehand. When COVID hit, we already had the foundation for telehealth centre visits, as well as home audio-visual visits. We had the technology, and a user-friendly application. UPMC is two or three steps ahead of other centres, and I think some of it is because so many people travel to see us, and we have experts in all fields. We use telehealth care with stroke care and ICU care, as there are many rural hospitals that need a lifeline to the bigger hospitals, rather than thinking that everybody needs to be transferred.

Another challenge going forward is how we can arm everybody with the appropriate device. Many of our rural patients don't have a device, or access to Wi-Fi. Many libraries and community centres have private rooms at their facilities for patients to go and have visits with their doctor. The device is there, and the Wi-Fi connection is good, versus always relying on the patient's home Wi-Fi and device. With the pandemic, those that had the technology were fine, and could access the visit, but it was a struggle for those that did not have an appropriate device and/or Wi-Fi connection.

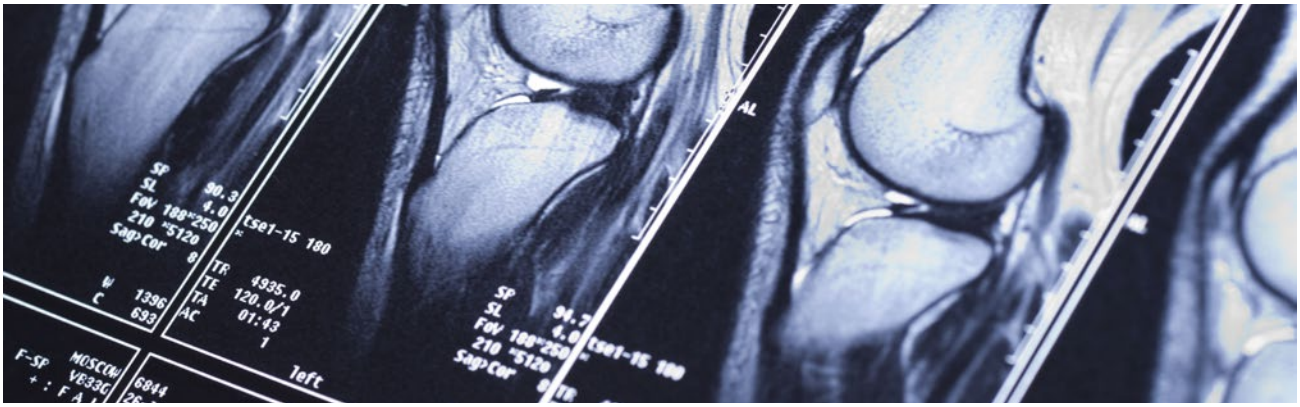
Q7 Are there any unique challenges and/or opportunities associated with practising as a rheumatologist in the USA compared to Europe?

I laughed a little bit at this question because I am not very familiar with rheumatology practices in Europe. I feel a big issue in the US is the cost of medications. I don't know if it's necessarily that much better in Europe, but in the US, it's atrocious. We always have the example outside of rheumatology of insulin and diabetes, but for us there are the biologic medicines. It's still such a struggle to get them approved and affordable for patients. And then a lot of times, it's just a "no". For our patients, because they typically have more than one thing going on, when they go to pay for medication, it really starts to add up for people, especially if they're on a fixed income. The approval process is a roadblock, with the paperwork and staff required. If people lose insurance, or their insurance plans change, or they lose their job, it's a big deal. I'm hoping it'll get better with the biosimilars that are emerging on the market.

Another huge issue, especially with telehealth, is medical licensure. Pennsylvania is a state that doesn't participate in the state licensure compact. Some states have no paediatric rheumatologists, and maybe only five or six adult rheumatologists. There are some states that maybe have one or two. And you think, why can't a rheumatologist in another state take care of these folks? Licensure is a big roadblock. I currently just have a license in Pennsylvania, so patients living in bordering states must travel. Because everything is focused on where the patient is rather than where the doctor is, some physicians choose to get licenses in different states. That starts to become very cumbersome because it must be renewed every year. For rheumatologists, if patients have more rare conditions, there could be nobody specialised enough in their state. We need to have relaxed licensure requirements, and I hope this changes. A lot of it has to do with money and insurance limitations, and I think that's one of the bigger considerations in the US.

Q8 Where will your clinical and research focuses lie in the coming years?

A lot of it will be trying to get to the crux of picking the type of visit; whether we can give providers some guidance about when to order something like an eConsult versus a regular visit versus the telehealth centre. Educating our own colleagues in rheumatology and referring providers about the many ways to see patients, and which option is most appropriate, is key. This could be different depending on the disease activity of the patient, and how they're doing. I also want to focus on arming primary care providers with more tools for appropriate rheumatology referrals. The primary care workforce has a great deal of turnover. When you think about the top reasons people go to any doctor, it is often joint pain, back pain, and fatigue. You can make a case that these reasons are all relevant to rheumatology, but there is no way we can accommodate all that as a specialty. That's a big challenge. And then training! Our rheumatology fellows need to know about these ways of telehealth care, even if most rheumatology fellows aren't going to focus on telehealth care modalities for the bulk of their career. However, even those who focus on clinical research or basic science research, need to recruit patients. Recruitment for clinical trials and research must consider virtual options.



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Q1 Your research focuses on pathogenesis, early recognition, and treatment of rheumatoid arthritis and systemic lupus erythematosus. Where did this interest come from?

Since I was in high school I have always found these topics very interesting. But I was also very interested in pathogenesis and wanted to know how biology works. I became a doctor because I really want to help people and I thought I could help people best by understanding the pathogenesis. If you understand how the disease works, you can probably intervene and I therefore chose to get a PhD in immunology. When I specialised in rheumatology, it was logical for me to see many patients with lupus, but the other big chunk of our business is patients with arthritis. I really wanted to understand how arthritis develops over time, so I started taking pictures of people at all stages of disease development, from healthy to arthrosis, to arthritis, and then the different chronic steps. I was very much inspired by the cancer field. With breast cancer for example, you can cut it out and be healthy, but if it has started traveling all over the body, it is a much bigger problem and you can die. I had a very similar picture for arthritis, specifically questioning how it develops over time, which steps are involved, and whether we can treat it. When I was still a fellow, my boss, who I am very grateful to, told me to pick a disease that nobody wants to see because others will be happy to refer their patients to you. So, I chose lupus because it was not very well understood as a disease.

Q2 You graduated from the University of Amsterdam medical school, the Netherlands, and then studied at Dartmouth medical school in New Hampshire, USA. How did this experience in the USA impact your future work and research?

In two ways I think. First of all, the scientific approach there was really focused on basic science. At the same time, what I like about the USA is that the sky is the limit, you can do anything. It is really the spirit of the people to be very driven. It was fantastic and I have really tried to keep that going.

Q3 You're currently the chairman of the National Post Graduate Educational Committee of Dutch Rheumatology. Could you tell us a bit about your role in that?

It is a group of about eight people from private practice and from academia and it's a very practical committee. I think it is always good in postgraduate education to consider what the people want to hear and what they consider important to learn about.

Q4 Over the years you've won many prizes. Which achievement are you most proud of?

Recently I got a European Research Council (ERC) grant, which is a very competitive grant and I am very proud of that. At the same time, the first prize I ever got was a national prize here in the Netherlands. Of course, I was much younger then and it was like Christmas as a child, we were really happy. So there were parallels in

the happiness I felt when I received this prize and when I received the ERC grant. It was also exciting for the field of rheumatology, because there are very few rheumatologists who have received such grants, so it also shows that our field has matured.

Q5 What do you believe are the biggest gaps in the current literature and which topics merit greater attention?

I think the biggest gap in the literature is how to fully understand the problems related to the patient. If you think about it, there have been 20 Nobel prizes in immunology, so we understand it quite well. We also understand what outcomes patients have such as swollen and painful joints. At the same time, there are other problems and patient reported outcomes, which have a big impact on them and we don't understand. For instance, a big problem for patients is being tired, and we don't understand that very well. I think the biggest gap in literature is understanding what the biology of certain parts of the phenotype is. If you don't understand how the biology works, it is very difficult to intervene. So, I really hope that in the next 5 years we get more insight into that. The other big problem is that we do not understand why the disease is chronic. Specifically, we do not understand the mechanism behind it. However, this is easier to understand from a biomedical point of view, compared to things like tiredness, so I think we will make more progress on this.

Q6 Are there any noteworthy projects you are currently involved in?

I am very much involved in research concerning the progression of arthritis. Specifically, we have identified a monoclonal antibody in patients, which is very predictive of arthrosis. Subsequently, we have identified a unique feature of this antibody. It is a little bit bigger than normal antibodies due to an extra sugar on the antigen binding site. The minute you develop the sugar, you can be sure that you will develop chronic arthritis over time. So, what we are trying to understand is the biology, how that works, and what kind of signal the sugar gives to the B cells.

Q7 As an educator, where can we expect to see your focus lie in the coming years?

I think clinical education is an enormously important issue. The good thing about being a clinician is that you improve over time. I am now 62 years old, and I have been doing this since I was 26 years old. My focus is on sharing my experience with younger doctors and I am doing that actively. I believe this is important because the holistic view of being a doctor is not easy to develop. When you first qualify, you have so much to focus on, it is easy to forget that the patient is more than a patient, they are also a human being. Essentially, I like to educate to people on the art of medicine.

"At the same time, what I like about the USA is that the sky is the limit, you can do anything."

Q8 Over the 30 years you have been practicing as a rheumatologist, how have you seen the field change, specifically with regard to the advancements in technology and therapies? What do you think has been the greatest development?

The biggest advancement is the better use of our drugs. When I started in rheumatology, I saw many patients in wheelchairs with rather horrible disease. Now, many people can live a normal life due to the proper use of anti-inflammatory drugs. The second big advance is targeted drugs. In the old days we tried many chemicals in the lab without exactly knowing how they were working. Then if it worked in animal models, you went to patients, which was really a trial-and-error process. What you see now is that we understand the biology much better. We know that this cell talks to the other cell via certain cytokines, so we can block these cytokines and expect the patient to get better.

Q9 How do you see these changes continuing and what future changes to you expect to see in the field?

Over the next 5 years we want to block chronicity so that arthritis is not a chronic disease anymore. I think that is the logical change we would want to see, as that means you can cure a disease. I really think we are on our way to achieve that, which is an enormous, fantastic thing.

Q10 Is there anything else you would like to add?

What I would like to add is that this career has brought me so much happiness. I still have very good friends from high school and university, who went on to become bankers or teachers, and say they look forward to retirement. I do not look forward to retirement at all as I love my job. So, what I would like to share is the enormous happiness you can get out of being a rheumatologist.

Evaluation of Xerostomia in Sjögren's Syndrome and Its Impact on Quality of Life and Nutritional Status: A Cross-Sectional Study

Editor's Pick

The quality of life of patients with primary Sjögren's syndrome is affected, and is often not considered regularly when managing them. This article by de Figueiredo et al. reports their study on the impact of xerostomia in patients with primary Sjögren's syndrome and those with systemic lupus erythematosus as a control group, using a questionnaire that included patient-reported symptoms. However, patients with systemic lupus erythematosus can also develop secondary Sjögren's syndrome. They found some preliminary interesting differences between the two groups, which warrants further study.

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Abstract

Background and aims: Patients with primary Sjögren's Syndrome (PSS) suffer from xerostomia, or dry mouth, which has been associated with oral/teeth disease and can compromise food intake, nutritional status, and quality of life (QoL).

Materials and methods: Cross-sectional study by mail of questionnaires with European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index (ESSPRI), Xerostomia Quality of Life Scale (XeQoLS), Primary Sjögren's Syndrome Quality of Life (PSS-QoL), food restrictions, and nutritional status questions, to the authors' patients with PSS, sicca, and systemic lupus erythematosus (SLE).

Results: A total of 46 patients responded: 19 patients with PSS, 13 with Sicca, and 14 with SLE. Patients with sicca were older. Patients with PSS and sicca had a higher ESSPRI dryness score. XeQoLs was higher in patients with PSS and sicca, but was similar in PSS-QoL. There was non-significant food restriction, higher in patients with PSS for sugary foods (58.0% versus 47.0% versus 36.0%; p=0.4), sticky foods (58.0% versus 54.0% versus 29.0%; p=0.2), meat/fish (26.0% versus 15.0% versus 0.0%; p=0.1), acidic beverages (63.0% versus 62.0% versus 29.0%; p=0.1) and dairy (47.0% versus 23.0% versus 29.0%; p=0.3). Average weight and BMI were similar, with higher prevalence in patients with sicca and SLE who are underweight (0.0% versus 7.7% versus 7.7%; p=0.5), and lower prevalence in patients with sicca and obesity (33.0% versus 7.7% versus 36.0%; p=0.1). Malnutrition Universal Screening Tool (MUST) score showed non-significant higher at-risk status for patients with PSS (42.0% versus 23.0% versus 21.0%; p=0.6).

Conclusion: Patients with PSS had lower xerostomia-related QoL, but similar overall QoL between groups. Reduction in food intake was higher in patients with PSS, and may be related to symptom management, but might lead to nutritional mistakes. A greater proportion of patients with PSS were overweight, but nutritional risk is still high. The authors' main issue is the small sample size.

Key Points

1. Xerostomia impacts food choice for patients with primary Sjögren's syndrome (PSS).
2. Quality of life related to xerostomia is lower in patients with PSS compared to those with systemic lupus erythematosus.
3. Nutritional status and risk should be part of the evaluation of patients with PSS, as well as nutritional advice.

INTRODUCTION

Primary Sjögren's Syndrome (PSS) is a systemic autoimmune disease characterised by lymphocytic infiltration of exocrine glands and clinically by the presence of sicca symptoms, inflammation of glands (mainly salivary and eye), and auto-antibodies.[1,2] Classification criteria have been proposed and take into account serology, histology of salivary glands, and functional tests of xerostomia and dry eyes.[1,3,4] Two scores, the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) and EULAR Sjögren's Syndrome Patient Reported Outcome (ESSPRI), have been validated to assess disease activity and symptom burden, respectively, in PSS.[5,6]

Sicca symptoms such as xerostomia result from inflammation and inflammatory destruction of the glands.

Mouth dryness affects oral health, with mouth and teeth disease, halitosis, and teeth loss, caused by dryness, change on the flora, and infections.[7] Xerostomia can also be aggravated by certain foods that are acidic, spicy, or dry.[8] Frail oral health, together with dryness, has been shown in a small cohort to have a vast impact on the patients' dietary habits.[9-11]

Salivary disfunction and oral health in PSS has been associated with lower quality of life, associating with salivary flow rate.[12-15]

However, there is still a gap in knowledge in the impact of xerostomia, oral health, and dietary habits in nutritional status and risk, and in the patient's quality of life (QoL). The aim of this article is to assess the impact of dry mouth and dietary habit changes on QoL and nutritional risk in patients with PSS.

METHODS

The authors performed a cross-sectional observational study of patients with PSS followed in the Autoimmune Disease Unit, Unidade de Doenças Autoimunes, Hospital Curry Cabral, Centro Hospitalar Universitário Lisboa Central, Portugal. The authors applied a questionnaire that included patient-reported symptoms using ESSPRI; oral dryness impact in QoL using XeQoLS; QoL in patients with PSS using PSS-QoL; and food intake and nutritional status.

The questionnaire was sent by mail, to be filled in by the patients, together with a presentation letter regarding the project, and informed consent for signing, as well as an envelope for return. Letters were sent for patients followed at the authors' unit with a diagnosis of PSS, sicca symptoms not fulfilling PSS diagnostic criteria (a positive controls of xerostomia), and those with systemic lupus erythematous (SLE), excluding those with secondary Sjögren's Syndrome (as controls).

After receiving the patients' questionnaire responses, the authors collected information on demographics and disease activity for each patient from electronic medical records. Nutritional status will be inferred by the Malnutrition Universal Screening Tool (MUST) score, performed through the nutritional status questionnaire answers.

The project was submitted to and approved by the Hospital Ethics Committee, and has maintained anonymity of participants.

Statistical Analysis

Sample size calculation yielded 80 participants, assuming a 5% margin error and 95% confidence interval, for a population of about 100 patients. Data was analysed by comparing the three different groups. Parametric data was expressed as mean (standard error of the mean), and non-parametric data as median (interquartile range). The authors performed a Student's t-test, Wilcoxon signed-rank test, or Analysis of Variance test for parametric data, and χ^2 test for non-parametric data, and Spearman's rank correlation coefficient for correlations. The authors performed the Bonferroni Correction if more than two groups were being compared.

Statistical analysis was performed using STATA (StataCorp LP, Stata Statistical Software: Release 14, College Station, Texas, USA). A p value of <0.05 was considered statistically significant.

RESULTS

A total of 109 patients fulfilled the criteria and were included in the study and sent letters: 30 patients with PSS, 20 with sicca syndrome, and 59 with SLE. Out of those, 46 patients responded: 19 patients with PSS, 13 patients with sicca, and 14 patients with SLE, yielding about a 40% response rate.

All patients were female, with patients with sicca being older and patients with SLE younger (62.0±10.0 versus 71.0±10.0 versus 55.0±9.8 years; $p<0.01$). Age at onset was similar between groups (46.0±11.0 versus 48.0±14.0 versus 45.0±13.0 years; $p=0.1$), which resulted in longer disease/symptom duration, though this was not significant (15.0±9.8 versus 23.0±10.0 versus 18.0±9.0 years; $p=0.058$). Regarding antibody prevalence, anti-nuclear antibodies were overall prevalent; however, anti-Sjögren's syndrome-related antigen A autoantibodies (63.0% versus 31.0% versus 21.0%; $p=0.03$) and anti-Sjögren syndrome type B antigen/Lupus La (42.0% versus 7.7% versus 21.0%; $p=0.08$) antibodies were more prevalent in patients with PSS.

Patients with PSS fulfilled the classification criteria in the following way: 74% fulfilled the American-European Consensus Group (AECG) 2002 criteria; 16% fulfilled the American College of Rheumatology (ACR) 2012 criteria; and 63% fulfilled the ACR/EULAR 2016 criteria. ESSDAI median was 0 (0–2), with 17 as the maximum score, showing a low activity of disease overall. Patients with SLE had a 1.5 (0–5) median SLE Disease Activity Index (SLEDAI), with 28 as the maximum score.

Quality of Life

Considering patient-reported symptoms using the ESSPRI score, patients with PSS and sicca had higher dryness scores (5.4±2.5 versus 5.4±2.5 versus 2.6±3.2; $p<0.01$), with similar fatigue and pain scores. QoL impact of dryness evaluated by XeQoLs revealed higher scores in patients with PSS and sicca symptoms in all

Table 1: Patient-reported symptoms by group.

	PSS	Sicca	SLE	Total	p
ESSPRI					
Dryness	5.4 (2.5)	5.4 (2.5)	2.6 (3.2)	4.6 (3.0)	0.010
Fatigue	5.3 (2.8)	6.7 (2.0)	6.0 (3.3)	6.0 (2.8)	0.400
Pain	5.8 (2.7)	6.8 (2.0)	6.3 (3.4)	6.2 (2.8)	0.600
XeQoLs					
Physical	5.7 (4.3)	5.0 (3.9)	2.7 (4.0)	4.6 (4.2)	0.100
Pain/discomfort	7.6 (3.8)	5.6 (3.4)	3.8 (4.4)	5.9 (4.0)	0.030
Psychological	7.4 (4.5)	5.5 (4.3)	3.5 (4.3)	5.7 (4.6)	0.050
Social	3.2 (3.0)	2.7 (3.3)	1.5 (2.4)	2.5 (2.9)	0.250
Total	24.0 (14.0)	19.0 (14.0)	12.0 (14.0)	18.8 (15.0)	0.058
PSS-QoL	48.0 (14.0)	48.0 (14.0)	42.0 (21.0)	46.0 (16.0)	0.500

ESSPRI: European League Against Rheumatism Sjögren's Syndrome Patient Reported Index; PSS: primary Sjögren's syndrome; PSS-QoL: Primary Sjögren's Syndrome Quality of Life; SLE: systemic lupus erythematosus; XeQOLS: Xerostomia Quality of Life Scale.

dominion, and, in total, although this was not always significant: physical (5.7±4.0 versus 5.0±3.9 versus 2.7±4.0; p=0.1), pain (7.6±3.8 versus 5.6±3.4 versus 3.8±4.4; p=0.03), psychological (7.4±4.5 versus 5.5±4.3 versus 3.5±4.3; p=0.05), social (3.2±3.0 versus 2.7±3.3 versus 1.5±2.4; p=0.25), and total (24.0±14.0 versus 19.0±14.0 versus 12.0±14.0; p=0.058 [Table 1]).

QoL assessed by PSS-QoL was similar between the three groups (48.0±14.0 versus 48.0±14.0 versus 42.0±21.0; p value=0.5). Dryness from the ESSPRI scale correlated with both XeQoLs and PSS-QoL with significance (p<0.001 [Table 1]).

Dietary Intake and Nutritional Status

As for dietary intake, all patients reported some degree of reduction of intake due to their condition/symptoms. The most frequent were acidic beverages (52%); sugary, sticky, or spicy foods (48%); and fried food and alcoholic beverages (46%). Although there was no significant difference between the three groups, in some food categories there was a greater decrease of intake in patients with PSS and sicca: sugary foods (58% versus 47% versus 36%; p=0.4); sticky foods (58% versus 54% versus 29%; p=0.2); meat/fish (26% versus 15% versus 0%; p=0.1); acidic beverages (63% versus 62% versus 29%; p=0.1); and dairy (47% versus 23% versus 29%; p=0.3 [Table 2]).

Self-reported data of height and weight showed similar average weight in the groups (68.0±10.0 versus 62.0±7.8 versus 71.0±29.0; p=0.4) and BMI (27.0±4.6 versus 25.0±3.5 versus 27.6±9.6; p=0.5). Although not significant, there were some differences in BMI category: higher prevalence in patients with sicca and SLE who were underweight (0.0% versus 7.7% versus

Table 2: Food intake restrictions and nutritional status.

	PSS	Sicca	SLE	Total	p
Food restrictions					
Sugary	11 (58%)	6 (47%)	5 (36%)	22 (48%)	0.4
Sticky	11 (58%)	7 (54%)	4 (29%)	22 (48%)	0.2
Spicy	8 (42%)	7 (54%)	7 (50%)	22 (48%)	0.7
Fried	9 (47%)	7 (54%)	5 (36%)	21 (46%)	0.6
Vegetables/fruit	2 (11%)	2 (15%)	1 (7%)	5 (11%)	0.7
Meat/fish	5 (26%)	2 (15%)	0 (0%)	7 (15%)	0.1
Rice/pasta	4 (21%)	1 (7%)	2 (14%)	7 (15%)	0.5
Acidic beverages	12 (63%)	8 (62%)	4 (29%)	24 (52%)	0.1
Alcoholic beverages	9 (47%)	7 (54%)	5 (36%)	21 (46%)	0.6
Caffeinated beverages	7 (37%)	3 (23%)	3 (14%)	12 (26%)	0.3
Dairy	9 (47%)	3 (23%)	4 (29%)	16 (35%)	0.3
Nutritional status					
Weight	68.0 (10.0)	62.0 (7.8)	71.0 (29.0)	68.0 (18.0)	0.4
BMI	27.0 (4.6)	25.0 (3.5)	27.6 (9.6)	26.8 (6.0)	0.6
Underweight	0.0 (0.0%)	1.0 (7.7%)	1.0 (7.1%)	2.0 (4.4%)	0.5
Overweight	10.0 (56.0%)	8.0 (62.0%)	8.0 (57.0%)	26.0 (58.0%)	0.9
Obesity	6.0 (33.0%)	1.0 (7.7%)	5.0 (36.0%)	12.0 (27.0%)	0.1
MUST score					
Low risk	11 (58.0%)	10 (77.0%)	11 (79.0%)	32 (70.0%)	N/A
Medium risk	4 (21.0%)	1 (7.7%)	1 (7.1%)	6 (13.0%)	N/A
High risk	4 (21.0%)	2 (15.0%)	2 (14.0%)	8 (17.0%)	N/A

MUST: Malnutrition Universal Screening Tool; N/A: not applicable; PSS: primary Sjögren's syndrome; SLE: systemic lupus erythematosus.

7.7%; p=0.5), and lower prevalence in patients with sicca in obesity (33.0% versus 7.7% versus 36.0%; p=0.1 [Table 2]).

MUST score was calculated by using the patients' BMI, percentage of recent weight loss, concomitant presence of acute illness, and reduction of food intake. Most patients were on the low-risk strata (58.0% versus 77.0% versus 79.0%); however, more patients with PSS were at risk, either medium (21.0% versus 7.7% versus 7.1%) or high (21.0% versus 15.0% versus 14.0%), even if not significantly (p=0.6 [Table 2]).

DISCUSSION

The authors' sample, despite its small size, was overall representative of the population with Sjögren's syndrome in its demographics.

The group with sicca symptoms is suggestive that sicca symptoms might be age-related rather than autoimmune in nature. As always, classification criteria raise discussion as they do not seem to be optimal in specificity and sensitivity for all patients, suggesting some patients in the sicca group may have PSS, even though they do not fully fulfill any of the classification criteria.

The authors' cohort, as with most patients with PSS, has a very low disease activity score, with complaints being most related to dryness and fatigue symptoms. This idea was further confirmed by the ESSPRI score results. It was interesting to observe that both pain and fatigue domains were similar between the three groups: patients with sicca, being older, will experience pain and fatigue related to degenerative conditions, and muscular pain, articular pain, and fatigue can be an important feature in SLE. As expected, dryness score was higher in patients with PSS, but also patients with sicca (the authors' positive control for dryness), and lower in patients with SLE, after excluding those with secondary Sjögren's syndrome.

Patients with PSS had higher XeQoLS scores, which corresponds to a lower QoL compared to both patients with sicca and SLE. The domains with greatest impact of xerostomia on QoL were pain and psychological, which may give clues on approaches to improve QoL. It is interesting to observe that patients with sicca have worse xerostomia-related QoL than patients with SLE, but still better than patients with PSS. However, when QoL was assessed directly with PSS-QoL, all groups were similar, which may relate to overall poor QoL in these three groups, but also the lack of specificity of this questionnaire. Interestingly, both questionnaires correlated with dryness from ESSPRI, showing the importance of symptom control for patients' wellbeing.

All groups had some reduction of food intake related to their symptoms, and although not significant, some food categories were more frequent in patients with PSS. Some of these food restrictions are beneficial and recommended for symptom control, since some foods (acidic, spicy, and fried) worsen xerostomia, or may aggravate oral health (sugary food). The authors observed such a pattern from patients with PSS. However, other food restrictions are not recommended in symptom control and may contribute to risk of malnutrition, such as meat/fish and dairy restriction. These observations show the importance of patient health education, with dietary and even cooking suggestions to ensure correct and balanced feeding, while also contributing to symptom control and patient satisfaction.

Regarding nutritional status, there was not a single patient with PSS in the underweight BMI category; however, there was a higher prevalence in the obesity category. Patients with obesity, although usually known by its over-nutritional status, often have malnutrition features such as sarcopenia and micro-nutrient deficits, which are overlooked and potentially health hazards. Remarkably, 42% of patients with PSS were at risk, compared to 23% and 21% from the sicca and SLE group, respectively, which should raise a red flag.

Comparing these results to a similar study with 25 patients of the Sjögren's Newcastle cohort, the group had larger percentages of restriction in foods that worsen the symptoms, such as acidic, spicy, and sugary.[9] This probably reflects the patient health education programmes at this institution. However, patients had similar restriction of meat/fish. Average BMI was similar; however, the Newcastle cohort had a higher prevalence of overweight patients (70% versus 56%), which can be representative of obesity differences between countries. Also contrasting was the nutritional risk of 42% in the authors' cohort, versus 18% in the Newcastle cohort.

The authors' work had several issues. The main one is the small sample size, lower than sample size calculations, which compromised results and conclusions. It resulted both from initial small cohorts, but also from the method of applying the questionnaire with a 40% response rate. Even though a 40% response rate is high for questionnaire standards, the authors could have increased it by personally applying the questionnaires in clinic appointments. The sample size could also be increased by adding other centres to the cohort. Another issue was that weight and height data was self-reported, which could have included several errors and may contribute to report bias. Furthermore, nutritional assessment without personal evaluation is very lacking and, in the future, should include bioimpedance and laboratory analysis.

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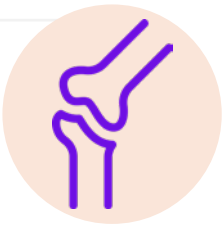
An Update on Medication-Related Osteonecrosis of the Jaw in Patients with Osteoporosis



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Abstract

Medication-related osteonecrosis of the jaw (MRONJ) is a feared complication of anti-resorptive or anti-angiogenic therapy, presenting with non-healing areas of bone, which may form *de novo* or after dental intervention. The condition primarily affects patients under the care of oncologists and rheumatologists. Patients using these medications under the care of rheumatologists are predominantly being treated for osteoporosis, a highly prevalent condition causing considerable morbidity and mortality in the European population.

In the two decades since the condition was first described, there has been considerable progress in the understanding of the pathophysiology of the condition, although this remains incomplete. Additionally, clinicians may now benefit from long-term follow-up data to give a more evidence-based approach to MRONJ risk stratification. At present, there is considerable variation between guidelines produced by advisory groups. This paper focuses exclusively on the osteoporotic cohort, and aims to review recent findings to explore the differences in risk profiles between osteoporotic and oncological cohorts, as well as between different anti-resorptive medications. Further sections discuss prevention and management of MRONJ in osteoporosis, including the timing of tooth extraction, and consider the direction of future research. The findings suggest that patients with osteoporosis treated with bisphosphonates carry an extremely low risk of MRONJ, although

denosumab presents a higher risk. Nevertheless, the reduced fracture rate from prompt treatment with anti-resorptives likely outweighs the risk of MRONJ. Dental hygiene should be optimised to reduce risk, and tooth extraction should take place in a timely fashion, with no convincing evidence to support the use of drug holidays. Treatment at present favours a surgical approach, with potential roles for antibiotics, but at present there is insufficient evidence for other medical adjuncts.

Key Points

1. Patients with osteoporosis should be recognised as being at considerably reduced risk of medication-related osteonecrosis of the jaw (MRONJ) relative to oncology patients, and risk stratified accordingly to avoid unnecessary delays to treatment.

2. The route and duration of antiresorptive administration appears not to significantly affect the risk of MRONJ, but there is a dose-dependent risk, which does not appear to be reduced by a drug holiday.

3. Tooth extraction is recommended if required, without delay. Higher risk patients should have extraction performed under the care of a maxillofacial service, and all patients with established MRONJ should also be referred.

INTRODUCTION

Osteoporosis is a common disease, with a mean prevalence of 5.6% within European (EU27+2) countries, and an annual cost to these countries of EUR 56.9 billion.[1] This figure is illustrative of the significant morbidity and mortality burden associated with these fractures. As the population of Western Europe ages, preventing and treating this often debilitating condition continues to gain ever-greater importance.

It has become apparent, however, that treatment or prophylaxis of osteoporosis may be associated with medication-related osteonecrosis of the jaw (MRONJ), predominantly occurring in patients with cancer or osteoporosis, as a rare but debilitating side-effect of anti-resorptive or anti-angiogenic therapy, although the latter group is beyond the scope of this paper. MRONJ is a relatively recently described phenomenon, first appearing in the medical literature in 2003 as part of a case series from Marx et al.[2] Since the initial description, there have been considerable advances in the understanding of the condition, which may inform changes to current practice for clinicians involved in the care of patients with osteoporosis. The condition is most frequently described in patients in oncology and osteoporosis. This paper aims to highlight the changes in evidence impacting current clinical practice in the prevention and management of MRONJ in relation to osteoporosis, as the two groups have different risk profiles, and the approach to osteoporosis is often conflated with that for the oncology population.

The first cases described were in association with nitrogen-containing bisphosphonates, which act to inhibit the mevalonate kinase pathway to induce osteoclast apoptosis. Bisphosphonates remain the most commonly reported cause of MRONJ. The disease occurs preferentially in the mandible rather than the maxilla, at a ratio of approximately 2:1, with 9% of cases having involvement at both sites.[3] Since the inaugural paper, further definitive associations have been made with other anti-resorptive medications, particularly the receptor activator of nuclear factor κ-B ligand inhibitor denosumab, but also the newer anti-sclerostin agent, romosozumab.[4,5]

The American Academy of Oral and Maxillofacial Surgeons (AAOMS) have set widely accepted diagnostic criteria for MRONJ, which needs to fulfil all three of the following criteria to make a diagnosis:[6] current or previous use of anti-resorptive therapy alone, or in combination with immune modulators or anti-angiogenic medications; exposed bone in the maxillofacial region persisting for more than 8 weeks, either visualised directly, or discovered via probing

oral fistulae; and the absence of significant radiation exposure or metastatic disease of the affected area.

The clinical course is variable, and many patients remain asymptomatic for prolonged periods. However, pain; gingival inflammation, ulceration, and fistulation; bony enlargement; tooth loosening; and secondary osteomyelitis may occur.[7] Treatment is extremely challenging and may involve both medical and surgical approaches. Prevalence is highest in the oncology population, thought to be a dose-dependent result of the high cumulative dosages used to limit bony destruction or control malignant hypercalcaemia, with typical dosing regimens resulting in administration of doses 12–15 times higher per annum than those used in osteoporosis.[8] These drugs are also widely used within rheumatology services for metabolic bone disease, most frequently in the case of primary osteoporosis, but also for the purpose of treatment or prophylaxis of secondary osteoporosis, typically where prolonged treatment with steroid therapy is required. Anti-resorptives also find usage in rarer metabolic bone disease such as Paget's disease of bone, fibrous dysplasia, and osteogenesis imperfecta. Thus, consideration of risk of MRONJ presents a frequent challenge for the rheumatologist, and requires interdisciplinary collaboration with maxillofacial and dental colleagues.

IDENTIFICATION AND MANAGEMENT OF HIGH-RISK PATIENTS

Risk Stratification

Recent evidence, collated in the 2022 AAOMS update, suggests that, as a consequence of the high estimated MRONJ prevalence of 1–17% in the oncology population, the risks of MRONJ may have received undue prominence in patients receiving the medication for other indications.[6,9] This may have come at the cost of an increased number of fragility fractures in the face of patient and physician reluctance to use anti-resorptives in a timely fashion on this basis. The low prevalence of MRONJ should be contrasted with the results from a large-scale meta-analysis performed by Crandall et al.,[10] which indicated a number needed to treat of between 30–89 for denosumab and bisphosphonates over the first 1–3 years of treatment, depending on fracture site and gender. Although the number needed to treat may appear relatively high, the high prevalence and severe morbidity and mortality of osteoporotic fracture must be taken into account. If osteoporotic treatment is delayed by screening and assessment, there is considerable risk of subsequent preventable fractures.

Increasing duration of therapy has been shown to correlate significantly with incidence of MRONJ in oncology patients. However, the data for osteoporotic patients is less clear. Initial support was found from a paper undertaking retrospective case identification via a postal questionnaire, demonstrating an increase from 0.00% prevalence at baseline to 0.21% prevalence at 4 years for patients on oral bisphosphonates. Subsequent prospective controlled cohort studies failed to demonstrate the same findings, although it should be noted that these were neither designed nor powered to assess MRONJ cases.[6] Both bisphosphonates and denosumab now benefit from long-term follow-up data, enabling accurate assessment of prevalence, which is challenging existing assumptions. The prevalence of MRONJ in patients exposed to bisphosphonate ranges from 0.02–0.05%, with zoledronate showing no higher risk than oral bisphosphonates. Denosumab demonstrates a 10-year prevalence of 0.30%, and the current emerging data on romosozumab suggest that there is a prevalence of 0.02–0.03%.[6] Given that many guidelines continue to consider intravenous bisphosphonates to be higher risk, this suggests that dose, rather than route, is the differentiating factor.

Nevertheless, patients with osteoporosis are not a homogenous group. While the majority of those treated will have primary osteoporosis, patients with osteoporosis related to a rheumatic inflammatory disease (either the disease itself or the treatment thereof, e.g., where prolonged treatment with steroids is required) may be at higher risk of MRONJ, with one study demonstrating a 1.5% prevalence of MRONJ in this group (n=198).[11] This has a plausible mechanism; rheumatic inflammatory diseases, particularly rheumatoid arthritis, are known to be associated with MRONJ risk factors such as periodontitis.[9] Glucocorticoids are well known to be a cause of osteoporosis,

but are also a risk factor for MRONJ. As part of the wide-ranging effect of administration of glucocorticoids, osteoporosis is thought to relate not only to induction of osteoblast apoptosis, but also to inhibition of osteoclast function via a separate pathway to each anti-resorptive, compounding existing issues of reduced bone turnover.[12] This also applies to another putative mechanism of MRONJ, reduced angiogenesis. Glucocorticoids have also been shown to reduce vascular endothelial growth factor expression, again amplifying anti-angiogenic effects of bisphosphonates and denosumab, which have been demonstrated *in vivo* through murine models, contributing to emerging necrosis.[13,14] Larger multicentre studies would be required to more definitively evaluate the influences of rheumatic inflammatory disease and the medications used to treat them, which may influence stratification of non-oncological patients.

Finally, poor oral health at the time of commencing therapy is a key risk factor for MRONJ. A 2005 paper from Marx et al.[15] demonstrated, from a sample of 119 patients with MRONJ, a considerably higher prevalence of periodontitis (84.0%), caries (28.6%), and dental abscess (13.4%) than the general population. Tooth extraction has classically been considered the key risk factor for MRONJ, but again, the osteoporotic population are at considerably lower risk, with a meta-analysis by Gaudin et al.[16] demonstrating a 0.15% rate of MRONJ (p=<0.0001) in this cohort after tooth extraction. While no comparison study for conservative and surgical strategies has been performed in osteoporotic patients, a dual-centre study of 189 oncology patients demonstrated a dramatic difference in MRONJ development after propensity matching. Those in whom tooth extraction was avoided demonstrated approximate rates of 90% MRONJ occurrence by 8 years, but those who underwent tooth extraction displayed rates of <20%, although all cases in the latter group occurred within 2 years.[17] This would support the hypothesis that local inflammation or infection is a predominant driver of MRONJ, and the requirement for extraction is a symptom of the conditions favouring MRONJ, rather than the direct cause.

This view is supported by the observation that pre-existing periodontal or periapical disease without any oral intervention/trauma is sufficient to cause spontaneous MRONJ in approximately 25% of identified patients,[18,19] as well as the relatively minor trauma caused by ill-fitting removable dentures, especially at the retromylohyoid fossa.[19]

Prevention of Medication-Related Osteonecrosis of the Jaw

The field currently suffers from a lack of high-quality studies in order to assess the benefit of preventative procedures. A Cochrane review from 2017, subsequently updated in 2022, found insufficient evidence to support the conclusion that any studied prophylactic or therapeutic intervention is of benefit in MRONJ.[20] But, as tooth extraction and periodontal disease are the most common risk factors for developing MRONJ, prevention is predominantly targeted towards optimising oral health and modulating modifiable dental (e.g., extraction versus root-retentive treatment) or medical risk factors (e.g., review of anti-resorptive/anti-angiogenic and corticosteroid treatment).[21]

Routine screening of at-risk patients is recommended across several international consensus statements on the prevention and management of MRONJ.[6,22,23] The Scottish Dental Clinical Effectiveness Programme (SDCEP) recently updated their National Institute for Health and Care Excellence (NICE)-accredited guidance in the oral health management of patients at risk of MRONJ to stratify patients into low and high-risk groups.[24] The high affinity of bisphosphonates to hydroxyapatite results in a persistent dose-dependent effect that can last up to 10 years, whereas denosumab is cleared through the reticuloendothelial system with a half-life of approximately 26 days.[25,26] This is reflected in the SDCEP guidance, which stratifies low-risk patients as those taking denosumab for any length of time, whereas patients on oral or intravenous bisphosphonate become high-risk with over 5 years of use.[24] Indeed, after 9 months without denosumab, SDCEP classify the patient as having no risk of MRONJ.

Some authors advocate an aggressive approach to maintaining oral health in at-risk patients, with 5,000 ppm fluoride toothpaste and overnight fluoride gel bathing of equivocal prognosis dentition.[27] Following on from this, dental treatment, including dentoalveolar surgery, should proceed as normal for all patients, with the caveat of aiming for root retentive treatment in high-risk patients if possible, although protocols remain unstandardised.[28-30] A non-healing extraction site of over 8 weeks necessitates maxillofacial referral. The role of peri-/post-exodontia antibiotics in preventing MRONJ is controversial. In a systematic review by Cabras et al.,[31] only one out of 17 studies found a higher risk of MRONJ without antibiotics.

So-called 'drug holidays', referring to temporary discontinuation of bisphosphonates, remain a contentious issue regarding their benefit in either prevention or treatment of MRONJ. No consensus exists in adjudicating the balance between the risk of osteoporotic fractures with that of developing MRONJ. Patients using denosumab should not undertake drug holidays, as they are at increased risk of vertebral fractures if the drug is stopped: a post hoc analysis of the FREEDOM trial demonstrated an increased multilevel vertebral fracture rate that was apparent within 3 months after omission of a scheduled dose.[32]

A recent systematic review did not show any evidence for a bisphosphonate holiday in MRONJ.[33] Given the excess mortality of hip fracture at 1 year is up to 36%, the benefit of fracture prevention likely outweighs the low risk of MRONJ, and should be assessed using the Fracture Risk Assessment (FRAX) tool to help guide clinical decision making.[34,35] A reasonable compromise in patients taking denosumab, given the half-life and apparent increased risk relative to other anti-resorptives, is to plan dentoalveolar surgery for 3–4 months after the last denosumab dose, and resume 6–8 weeks post-surgery.[6]

It is important to acknowledge, however, that drug holidays remain appropriate for risk reduction of other complications associated with bisphosphonate therapy. A large retrospective Swedish study demonstrated a 70% annual reduction in adjusted odds ratio of atypical femoral fracture in bisphosphonate users since drug cessation.[36]

MANAGING PREVENTION OF MEDICATION-RELATED OSTEONECROSIS OF THE JAW

At present, it is inevitable that a small proportion of patients treated with anti-resorptives will go on to develop MRONJ. Management strategies for established disease are also required, which may be operative or non-operative in nature. If the patient has not already been referred to a maxillofacial team, this should, of course, be performed as a matter of urgency. Non-operative or operative strategies may be pursued at any point within the stages of MRONJ, depending on AAOMS staging (Table 1).

Certain measures are appropriate for all stages of MRONJ. All patients should receive education aiming to explain the slow rates of improvement and resolution over a period of months to years, and the intended aims of treatment, particularly symptom improvement and pain control. A cornerstone of therapy is improved oral hygiene, which may help those Stage 0 patients who will progress to the exposed bone variant, with one case series demonstrating a progression rate of 53.1%.[37] Mobile or well-formed bony sequestra should also be removed as a potential nidus for infection. Chlorhexidine solution should be used in all patients with established MRONJ, and may well prove sufficient for cure in Stage 1 patients when used as part of a local wound care strategy, aiming to disrupt the biofilm surrounding the necrotic bone and prevent progression of disease accordingly.[38] In Stage 2 or 3 disease, antibiotics and analgesia may be added.[6]

The rationale for antibiotic therapy relates to the key micro-organism group within the biofilm, *Actinomyces spp.* These facultative anaerobes are now thought to play a role in the pathogenesis of MRONJ, rather than just being a superficial contaminant. In a retrospective cohort study, Russmueller et al.[39] detected *Actinomyces spp.* in 89% of histologically confirmed MRONJ cases. β-lactam antimicrobials remain the agents of choice, with tetracyclines being an acceptable alternative in patients with penicillin allergy as *Actinomyces spp.* isolates have been shown to be almost uniformly resistant to metronidazole, and thus should be avoided.[39,40]

Although there is a debate regarding the timing

Table 1: Summary of American Academy of Oral and Maxillofacial Surgeons (AAOMS) staging criteria for medication-related osteonecrosis of the jaw severity.[6]

Stage	Criteria
0 (Non-exposed bone variant)	Patients with no clinical evidence of necrotic bone, but who present with non-specific symptoms or clinical and radiographic findings, the latter localised in alveolar bone only.
1	Exposed and necrotic bone or fistula that probes to the bone in patients who are asymptomatic and have no evidence of infection/inflammation. May have radiographic findings localised to the alveolar bone region, as in Stage 0.
2	As in Stage 1, but must be symptomatic, with evidence of infection/inflammation. These patients are symptomatic. May have radiographic findings localised to the alveolar bone region, as in Stage 0.
3	As in Stage 2, but with any of the following additional features: exposed necrotic bone extending beyond the region of alveolar bone, pathological fracture, extraoral fistula, oroantral/oronasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor.

of antimicrobials prior to surgery, high dose β-lactam antimicrobials in the days prior to surgery appears to be a reasonable strategy.[39]

Excellent results have been reported for surgical intervention, which may dramatically enhance resolution/improvement rates in comparison to conservative strategies.[6] The decision on when to undertake operative treatment should not be based solely on the clinical or radiological stage of disease, but also on the projected impact on quality of life, and capacity of the patient to undergo challenging bony and soft tissue reconstruction. Surgical options typically include initial debridement, saucerisation, or sequestrectomy in Stage 1 disease. The extent of mandibular or maxillary bony resection in Stage 1 and 2 disease largely depends on the height of disease-free alveolar bone available, and extent of disease in relation to the inferior alveolar nerve canal or maxillary sinus.[6] By definition, Stage 3 surgical management necessitates segmental resection or partial maxillectomy and appropriate reconstruction, but full discussion of reconstruction is beyond the scope of this article.

There is evidence to suggest early sequestrectomy and primary mucosal closure in Stage 1 disease can halt disease progression and even downstage lesions.[41,42] Vescovi et al.[43] have shown that conservative surgical interventions should be considered in patients unresponsive to 6 months of non-invasive therapy. In advanced disease, the controversy lies in when to surgically intervene. Debate still exists as to whether a period of non-operative therapy is beneficial in stabilising disease, as recommended in the AAOMS treatment algorithm, or whether aggressive primary surgery results in a shorter time to achieving restoration of mucosal integrity.[6] A recent systematic review compared surgical treatment options in Stage 3 disease.[44] With primary outcome measures, including full mucosal healing and disease downstaging, marginal resection without microvascular flap reconstruction resulted in a full mucosal healing rate of 85% compared with 54% with sequestrectomy alone. The addition of microvascular flap reconstruction resulted in a mucosal healing rate of 97%, likely due to the additional benefit of a segmental resection in more thoroughly removing all non-vital tissue. The success rates seen provide a firm mandate for surgical management being the mainstay of therapy at present.

A number of strategies have been trialled to improve non-operative treatment options. As with prophylaxis, no clear benefit to a

drug holiday of any anti-resorptive has been observed, and the majority of studies favour lack of benefit. While the prolonged half-life of bisphosphonates supports these results, the shorter half-life of denosumab, at just 26 days, would suggest a benefit to withdrawal.[45] However, in order to avoid rebound bone loss at discontinuation, a separate agent would need to be implemented. In the absence of MRONJ, denosumab cessation is now typically accompanied by zoledronate to maintain bone density gains from the period of denosumab therapy.[46] In a patient with established MRONJ, it is currently assumed that adding anti-resorptive therapy would be counterproductive. Withdrawal of anti-resorptives after confirmation of MRONJ, therefore, cannot be recommended at this stage in time, although further evidence may emerge, particularly surrounding romosozumab.

One therapy that has shown particular promise in improving MRONJ resolution rates is teriparatide, with Kim et al.[47] noting a statistically significant difference in the percentage of patients achieving resolution or improvement and also in rate of change over a 6-month period, albeit within a retrospective design. A further study suggested equivalence of weekly and daily injections, although with just one patient in each arm.[48] A placebo-controlled, prospective, randomised controlled trial of teriparatide failed to demonstrate statistical significance, which may have related either to the short duration of therapy of just 8 weeks, or to the small study size (n=34).[49] It would be tempting to consider the possibility of initiating teriparatide to continue treating both the MRONJ and osteoporosis and allow for denosumab cessation, but the DATA-Switch trial has provided evidence that teriparatide alone is insufficient to prevent bone loss after cessation of denosumab.[50] A high-quality prospective, randomised controlled trial, ideally with both weekly and daily administration arms, is required before teriparatide can be recommended as an integral part of medical management of MRONJ. After initial medical and surgical strategies have been implemented, patients must remain under close follow-up in order to assess response. At present, clinical history and oral examination, coupled with radiographic surveillance, are the mainstay of this process.

There has been some interest in the use of bone turnover markers to predict recovery, which have proved disappointing in predicting risk of MRONJ, where the majority of research attention has been focused.[51] One retrospective study found a statistically significant difference between the levels of bone turnover biomarkers of serum osteocalcin, C telopeptide, and bone alkaline phosphatase in patients who recovered and those who did not. However, the results should be interpreted with caution, given the trial design and absence of documentation of potentially confounding issues such as bony metastases, a particularly pertinent issue given the high numbers of oncology patients included.[52] Nevertheless, a sensitive and specific biomarker would be of great utility in guiding the ongoing management of these patients.

CONCLUSION AND KEY POINTS

Over the last 20 years, significant progress has been made in the understanding of the underlying pathophysiology of MRONJ. Nevertheless, our mechanistic understanding remains incomplete, and many clinical guidelines have not been recently updated to reflect the increased body of evidence available. As such, the authors would make the following suggestions for patients with osteoporosis:

- Unnecessary delays for routine dental review before starting bisphosphonates are likely to worsen outcomes, but regular dental review is important to optimise oral health and prevent MRONJ.
- The route and duration of anti-resorptive administration appears not to significantly affect the risk of MRONJ, but there is a dose-dependent risk.
- Tooth extraction is recommended if required, without delay. Higher risk patients should have extraction performed under the care of a maxillofacial service.
- There is limited evidence to support drug holidays for the purpose of decreasing MRONJ risk, but they do reduce the risk of atypical femoral fracture.

- Further research to stratify the risk of MRONJ within the osteoporotic cohort through study of rheumatic inflammatory diseases and drugs used to treat them would be highly beneficial.
- Surgical management remains the cornerstone of therapy. Antibiotics are the only medical adjunct with convincing evidence of benefit in MRONJ at present.

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