EMJ EUROPEAN MEDICAL JOURNAL

RHEUMATOLOGY

ISSN 2056-6395 — Vol 5.1 • July 2018 • europeanmedical-journal.com

INSIDE

Review of
EULAR 2018
Amsterdam, Netherlands

Contents

"The field of rheumatology is advancing at a blistering pace, with medical mysteries being unravelled every single day, and I look forward to the myriad of breakthroughs that this coming year will offer."

Spencer Gore, CEO

Editorial Board

VIEW IN FULL ←

Aims and Scope

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

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

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

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

EMJ also publishes 16 therapeutic area journals, which provide concise coverage of salient developments at the leading European congresses. These are published annually, approximately 6 weeks after the relevant congress. Further details can be found on our website: www.europeanmedical-journal.com

Editorial Expertise

EMJ is supported by various levels of expertise:

- Guidance from an Editorial Board consisting of leading authorities from a wide variety of disciplines.
- Invited contributors are recognised authorities from their respective fields.
- Peer review, which is conducted by EMJ's Peer Review Panel as well as other experts appointed due to their knowledge of a specific topic.
- An experienced team of editors and technical editors.

Peer Review

On submission, all articles are assessed by the editorial team to determine their suitability for the journal and appropriateness for peer review.

Editorial staff, following consultation with either a member of the Editorial Board or the author(s) if necessary, identify three appropriate reviewers, who are selected based on their specialist knowledge in the relevant area.

All peer review is double blind.

Following review, papers are either accepted without modification, returned to the author(s) to incorporate required changes, or rejected.

Editorial staff have final discretion over any proposed amendments.

Submissions

We welcome contributions from professionals, consultants, academics, and industry leaders on relevant and topical subjects.

We seek papers with the most current, interesting, and relevant information in each therapeutic area and accept original research, review articles, case reports, and features.

We are always keen to hear from healthcare professionals wishing to discuss potential submissions, please email: editorial.assistant@emjreviews.com

To submit a paper, use our online submission site: www.editorialmanager.com/e-m-j

Submission details can be found through our website: www.europeanmedical-journal.com/contributors/authors

Reprints

All articles included in EMJ are available as reprints (minimum order 1,000). Please contact hello@europeanmedical-journal.com if you would like to order reprints.

Distribution and Readership

EMJ is distributed through controlled circulation to healthcare professionals in the relevant fields across Europe.

Indexing and Availability

EMJ is indexed on DOAJ, the Royal Society of Medicine, and Google Scholar®; selected articles are indexed in PubMed Central®.

EMJ is available through the websites of our leading partners and collaborating societies.

EMJ journals are all available via our website: www.europeanmedical-journal.com

Open Access

Congress Notice

Staff members attend medical congresses as reporters when required.

This Publication

European Medical Journal Rheumatology is published once a year. For subscription details please visit: www.europeanmedical-journal.com

Front cover and contents photograph: Amsterdam, Netherlands, home of the EULAR 2018 Congress.

EMJ Rheumatology

European Medical Journal 3.1

This edition is packed with an assortment of peer-reviewed articles from a body of therapeutic areas, including reproductive health, dermatology, and cardiology, to name a few.

VIEW ALL JOURNALS ←

Welcome

It is with great pride that I present to you this year's edition of *EMJ Rheumatology*. The range of content in this eJournal has made it a real pleasure to compile; from the latest research revelations from the European League Against Rheumatism (EULAR) Congress to peer-reviewed articles covering the discipline's hottest topics, *EMJ Rheumatology 5.1* has something for everyone to enjoy.

Beautiful as ever in the spring sun, Amsterdam, Netherlands hosted this year's EULAR Congress, with an extensive programme featuring unique sessions in a plethora of formats. The highlights from this monolithic congress can be found within the journal's Congress Review section, including a selection of gripping abstract reviews penned by the presenters themselves. This year also saw EULAR celebrate the great success of its ongoing 'Don't Delay, Connect Today' campaign, which seeks to highlight the paramount importance of early diagnosis for musculoskeletal diseases. *EMJ Rheumatology 5.1* includes a special feature showing the incredible reach of this campaign, wherein Dr Louise Bennett of Rheumatosphere, University of Glasgow, Glasgow, UK recounts her team's EULAR-funded cycle ride across the Outer Hebrides, carrying the campaign's important message to some of the most remote parts of the UK. The Interviews section of the journal shares this theme of increasing awareness of rheumatological conditions and expanding the reach of care. In this section, *EMJ Rheumatology* Editor-in-Chief Dr Ian Chikanza discusses his pioneering work in increasing access to rheumatology care in Africa, an area of great unmet need regarding specialist rheumatological care.

As always, this eJournal finishes with a wonderful selection of peer-reviewed articles, covering topics from biosimilars to Janus kinase inhibitors, as well as the treatment and screening of rheumatoid arthritis, an area that has had a great deal of progress. As our understanding of musculoskeletal diseases and inflammation increases, so too does the necessity for a multidisciplinary approach. Inflammatory conditions have a great impact on the pulmonary, cardiac, renal, vascular, and ophthalmic systems; thus, collaboration between disciplines will be vital to the future of this fascinating therapeutic area.

Creating *EMJ Rheumatology 5.1* has been a real pleasure and I would like to heartily thank everyone who has contributed to its production. The field of rheumatology is advancing at a blistering pace, with medical mysteries being unravelled every single day, and I look forward to the myriad of breakthroughs that this coming year will offer.

Warm regards,

Spencer Gore

Chief Executive Officer, European Medical Group

Foreword

A warm welcome to this year's stimulating fifth edition of *EMJ Rheumatology*, which reviews the scientific data on the latest developments on the pathophysiology of, and targeted therapeutic approaches for inflammatory rheumatic and musculoskeletal diseases (iRMD). The past few years have been very exciting for rheumatology patients, especially the development of targeted therapies using monoclonal antibodies (mAbs) such as anti-TNF biodrugs targeted at specific sites of the inflammatory cascades and the introduction of small chemical molecules such JAK kinase inhibitors (Jakinibs) targeting the intracellular JAK kinase signalling pathway (JAK1, JAK2, JAK3, Tyk2). In contrast to current mAbs which target one site or cytokine, Jakinibs suppress a number of cytokines that are linked to inflammation.

The past few years have been very exciting for rheumatology patients, especially the development of targeted therapies using mAbs such as anti-TNF biodrugs targeting specific sites of the inflammatory cascades and Jakinibs targeting the intracellular JAK kinase signalling pathways...

The Editor's Pick in this issue is "JAK inhibitors in the Treatment Algorithm of Rheumatoid Arthritis: A Review". There is no doubt that other inflammatory conditions beyond rheumatology will also benefit from this medical innovation. The two licensed Jakinibs, tofacitinib and baricitinib, have similar efficacy to anti-TNF biodrugs. Other Jakinibs, such as peficitinib, filgotinib, decernotinib, and upadacitinib, are in clinical trials with promising results. One would have expected these oral chemicals to be cheaper than biodrugs; however, sadly, at present, the prices are similar to that of originator biodrugs, making this technological leap still out of reach to many.

"There is no doubt that other inflammatory conditions beyond rheumatology will also benefit from this medical innovation."

The patents of some anti-TNF biodrugs have expired, making it possible to produce copy-cat biodrugs now commonly referred to as 'biosimilars'. These are more affordable versions of originator mAb drugs. In this issue, we present a very comprehensive overview on the controversies associated with biosimilars, covering issues of switching, immunogenicity, regulatory aspects on interchangeability *inter alia*.

The search for other novel therapeutic targets continues. The role of the coenzyme nicotinamide adenine dinucleotide has extended from just cellular metabolism to immune-mediated inflammation in RA, therefore making it a potential therapeutic target. Evidence to support this notion is expertly presented in this issue.

Systemic lupus erythematosus continues to be a challenge. Active disease leads to major target organ damage. Targeting B cells with biodrugs such as rituximab and belimumab has proved to be very effective. A comprehensive review of relevant cytokines and associated inflammatory

mediators is presented within. This opens up other potential targets for drug development in this disease.

At the last international meeting of the European League Against Rheumatism (EULAR), in June 2018, in Amsterdam, Netherlands, we witnessed again an unprecedented number of pivotal clinical trials of new therapeutic entities as well as therapy optimisation strategies all continuing to be centred around the 'Treat-to-Target' approach whose main motto is aggressive early intervention to induce disease remission and prevent progression and development of long term morbidity and mortality. Some of the main highlights are reviewed in this issue.

Finally, I would like to highlight that awareness of iRMD in Africa is sparse and there are extremely few rheumatologists in Africa. As a result, many patients do not have an appropriate diagnosis. I therefore appeal to all rheumatologists in the West to help our colleagues in Africa. Some of this will include supporting activities around World Arthritis Day (WAD), which will be held on the 12th October. This year sees the launch of the first WAD Africa Conference, Victoria Falls, Zimbabwe (10th–12th October). I invite you all to attend this event, which will offer a unique opportunity to network with and to support physicians with an interest in RMD in Africa.

› See https://www.saraa.co.za/Content/Images/WAD_Africa_Conference_2018.pdf and https://www.arthritiscareafrica.org/wad-africa-conference

"...the boundaries for disease remission continue to be extended all the time. This has brought direct clinical benefits to patients."

I am very happy for our patients because in the last few years we have witnessed major strides in the management of rheumatic conditions and the boundaries for disease remission continue to be extended all the time. This has brought direct clinical benefits to patients. I am very pleased to present to you the fifth edition of *EMJ Rheumatology.* I sincerely hope that you will enjoy this latest edition and continue to find it a positive significant drive in your own thinking and work in the rheumatology field. To conclude, I would like to invite you to attend the next 2019 EULAR meeting in Madrid, Spain.

With kind regards,

Ian C. Chikanza

Barts and The Royal London Hospital, London, UK

Congress Review

Review of the 19th EULAR Annual European Congress of Rheumatology

Location: Amsterdam RAI Exhibition and Convention Centre - Amsterdam, Netherlands

Date: 13.06.18 – 16.06.18

Citation: EMJ Rheumatol. 2018;5[1]:10-24. Congress Review.

Almost 20 years have passed since the first annual European League Against Rheumatism (EULAR) Congress took place on the sunny shores of the French Riviera in Nice. Since then, much has changed. The event has grown immensely, both in terms of participants and the breadth of research on offer; technology has been increasingly integrated to create a fully interactive experience; and, of course, the field's understanding of rheumatic conditions has improved dramatically. However, one thing remains the same: the passion and dedication for improving the lives of patients.

The 19th Annual EULAR Congress was hosted in Amsterdam, Netherlands, a city famous for its myriad of waterways that dissect and connect the historic capital. In a sense, this aspect of the city embodied one of the central themes of the congress itself: connectivity. This year saw the EULAR organisers celebrate an inaugural year's success for the 'Don't Delay, Connect Today' campaign, which aimed to raise awareness of rheumatic conditions to encourage earlier diagnosis for better outcomes. Part of this campaign involved an exhilarating bike ride across the Scottish Hebrides to spread knowledge to one of the most isolated areas of the UK, and a summary of this exciting expedition can be found in the following pages.

The opening ceremony itself saw the EULAR President, Prof. Johannes W. J. Bijlsma, speak on a variety of subjects, praising the scope of the event's scientific programme and the success of the 'Don't Delay, Connect Today' campaign, as well as setting out the impressive goals for the coming years, primarily centred around education. "Education is one of the most important things we are working on. We made a nice text for the formulation of this goal: By 2023, EULAR will be (or stay) the leading provider of education in rheumatic and musculoskeletal disease." When asked if this goal will result in the EULAR Congress's evolution, Prof Bijlsma reiterated the intention of the event's

organisers to always improve the congress year after year, striving to create the most dynamic programme and the best environment for the sharing of rheumatological data.

As well as looking to the future, the EULAR Congress, as ever, was a wonderful opportunity for the rheumatology community to revel in the successes of their peers. A huge array of abstract awards were presented, with each of the winners receiving €1,000; six winners were chosen for both basic and clinical research, three for the best Health Professionals in Rheumatology abstracts, and one for the best People with Arthritis/Rheumatism in Europe (PARE) abstract. As always, the EULAR Congress featured a strong focus on nurturing the next generation of rheumatologists and this was directly reflected in the awards ceremonies, with three medical students recognised for exceptional research.

This was a record-breaking year for the EULAR organisers in many ways, with 14,000 delegates in attendance from >120 countries and >5,050 abstract submissions. It speaks for the quality of research available in this field that >50% of those abstracts submitted were accepted for presentation and around 30% for publication; the finest 370 were hand-selected for oral presentation. The programme itself was vast, featuring >175 sessions, from expert-led symposia to hands-on workshops, and >560 speakers. While the sheer scale of this meeting could easily be intimidating, the popular What is New/How to Treat (WIN/HOT) track ensured that all delegates had quick and easy access to key sessions. Much of the fantastic research presented at this congress is recorded in the following pages in the form of Congress Highlights for you to enjoy. Whether you attended the congress and would like to refresh your memory, or are seeing the data for the first time, these highlights will surely get the creative juices flowing.

"By 2023, EULAR will be (or stay) the leading provider of education in rheumatic and musculoskeletal disease."

Comparison of Malignancy Rates Between Tocilizumab and TNF Inhibitors

CURRENT UNCERTAINTY surrounding the influence of biologic disease-modifying antirheumatic drugs (bDMARD) was the subject of one of the studies presented at the EULAR Congress. This study, which was reported in a EULAR press release dated 13th June 2018, compared tocilizumab (TCZ) to TNF inhibitors (TNFi) with regard to rates of malignancy, excluding nonmelanoma skin cancer, in patients with rheumatoid arthritis.

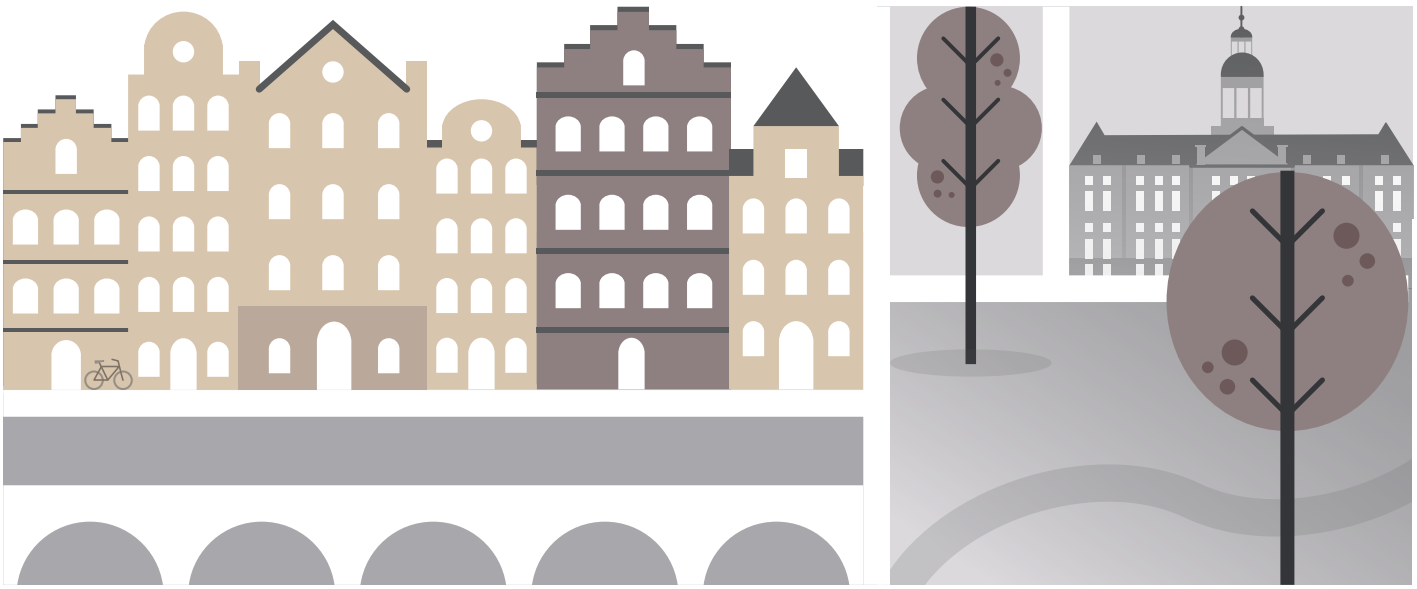
"With more biologic treatment options available and earlier initiation of therapy, it is important to understand the risk of malignancies in patients with rheumatoid arthritis."

It is important to study malignancy rates in patients with rheumatoid arthritis because this patient group is at an increased risk of developing certain types of malignancies, which is thought to be due to chronic inflammation and/or immune dysregulation. It is critical to consider bDMARD in relation to malignancy rates, as, due to their target-specific inhibition of the immune system, there are concerns that bDMARD may increase malignancy rates, and existing data on this subject are conflicting.[1] Therefore, as Prof Robert Landewe, Chairperson of the Scientific Programme Committee, EULAR, stated: "With more biologic treatment options available and earlier initiation of therapy, it is important to understand the risk of malignancies in patients with rheumatoid arthritis."

With such a goal in mind, the researchers designed a study to compare TCZ to TNFi. Patients included in the study were adults with rheumatoid arthritis who had recently started either TCZ or TNFi treatment regimens after treatment failure on abatacept, tofacitinib, or another TNFi. Using three healthcare claims databases, the researchers matched the propensity score of 10,393 patients who received TCZ to 26,357 patients administered TNFi. The primary outcome of the study was incidence of malignancy, not including nonmelanoma skin cancer. Malignancy was determined based on two diagnostic codes within 2 months. Individual secondary endpoints were incidences of the 10 most frequently occurring cancers, leukaemia, and human papilloma virus-related cancer. It was found that there were no statistically significant differences between the treatment groups for either the primary outcome or the secondary outcome, providing valuable information for healthcare practitioners when they are considering therapeutic options for rheumatoid arthritis.

References

1. Cho SK et al. The risk of malignancy and its incidence in early rheumatoid arthritis patients treated with biologic DMARDs. Arthritis Res Ther. 2017;19(1):277.



Intensive Treatment for Rheumatoid Arthritis Provides Long-Term Benefits

EARLY, intensive treatment of rheumatoid arthritis (RA) has been suggested to have long-term benefits for patients, including normalisation of mortality rates. According to a EULAR press release dated 13th June 2018, an avenue for the elusive improvement in RA patient mortality has been identified by a 23-year prospective study conducted by researchers at the VU University Medical Center, Amsterdam, Netherlands. Study author Prof Maarten Bowers, VU University Medical Center, commented on the novelty of the study: "Importantly, this study is one of the first to show a normalisation of RA mortality compared to the general population after 23 years of follow-up."

The initial COBRA study[1] included patients with early-stage RA who were randomised to receive either sulphasalazine (SSZ) monotherapy or SSZ in combination with low-dose methotrexate and initially high, step-down prednisolone. Combination therapy offered additional disease control compared to monotherapy. Follow-up 11 years later was carried out by another study and highlighted numerically lower mortality in patients receiving the combined therapy compared to the SSZ monotherapy; however, these results were not statistically significant.[2]

The study presented at the EULAR Congress included data from 154 of the original 155 patients, with a mean follow-up of 23 years. Results were compared with reference samples matched for age and sex. Again, a numerical lower mortality rate was found in the whole SSZ study population compared to the reference samples (28% and 35%, respectively). Within the study group, 27% of those randomised to the combined therapy died compared to 30% on SSZ monotherapy. However, neither of these results were statistically significant.

"...this study is one of the first to show a normalisation of RA mortality compared to the general population after 23 years of follow-up."

Study author Prof Bowers commented on the results: "Our results confirm that early, intensive treatment of RA, including use of glucocorticoids, has long-term benefits." Further studies are still warranted to elucidate a significant difference in mortality between mono and combined therapy; however, for the interim, these results are certainly encouraging and highlight a possible new therapeutic approach for those with this painful and debilitating disease.

References

1. Boers M et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet. 1997;350(9074):309-18.
2. van Tuyl LH et al. Survival, comorbidities and joint damage 11 years after the COBRA combination therapy trial in early rheumatoid arthritis. Ann Rheum Dis. 2010;69(5):807-12.

Zoledronic Acid Treatment Shows Promise for Mild Osteoarthritis

KNEE OSTEOARTHRITIS patients did not show significant symptom improvements following 1-yearly infusion of zoledronic acid (ZA); however, ZA may give symptomatic relief to patients with milder disease. According to the results reported in a EULAR 2018 press release dated 13th June 2018, the treatment did not significantly reduce bone marrow lesion (BML) size or knee pain in the study participants over 2 years, but ZA was effective in nonradiographic osteoarthritis patients.

"...there may be a role for ZA to relieve symptoms in patients with mild osteoarthritis."

An age-related disease that affects >40 million Europeans, osteoarthritis has a substantial societal impact and economic burden, which is expected to become more significant in the near future as life expectancy increases. Since the therapeutic options for the disease are limited, research has focussed on drugs that effectively reduce the frequent symptoms of joint pain and BML.

A previous pilot study showed promising results for knee osteoarthritis patients after ZA infusion over 6 months; in a cohort of 59 adults, knee pain and BML size were both reduced following ZA treatment. A multicentre, randomised, double-blinded, placebo-controlled trial presented at the EULAR 2018 Congress therefore aimed to build on these successful results by showing that the symptomatic improvements could be reproduced over a 2-year period in a larger cohort of 223 patients. The study participants, who had a mean age of 62 years and a slight female predominance of 52%, had significant knee pain defined by a visual analogue score (VAS) ≥40 mm and MRI-detected knee BML.

The patients were randomised to receive either ZA or placebo once-yearly, but the results showed no significant changes in symptoms after 24 months. For example, for knee pain, measured using the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC), scores were -37.5 versus -11.7 (p=0.205) and the VAS pain scores were -11.5 versus -16.8 (p=0.17) for the ZA and placebo groups, respectively. In addition, the knee BML sizes were -33.5 mm^2 versus 11.7 mm^2 (p=0.68) for the ZA and placebo patients, respectively.

However, ZA treatment of patients without radiographic osteoarthritis (joint space narrowing Grade 0) was more effective than placebo in prespecified analyses (WOMAC pain: -88.3 versus -42.6 [p=0.21]; VAS pain: -21.8 versus -8.3 [p=0.11]; and BML size: -67.4 mm^2 versus 98.2 mm^2 [p=0.14]). "It is disappointing that our results have not replicated the positive findings of the initial pilot study," commented Prof Graeme Jones, Menzies Institute for Medical Research, Hobart, Australia, who added: "However, there may be a role for ZA to relieve symptoms in patients with mild osteoarthritis."

Canakinumab Cuts Gout Flare Rates in Patients with Atherosclerosis

"OUR RESULTS demonstrate a striking effect of canakinumab on reducing the risk of gout attacks in atherosclerosis patients," commented Prof Daniel Solomon, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts, USA, speaking about the results of a secondary analysis of CANTOS trial data he was part of. These results were reported in a press release from the EULAR Congress, held from 13th–16th June 2018.

Gout is a very common condition; therefore, any insight that can be obtained, which may aid treatment, is of great utility. The researchers set out to examine the impact of canakinumab, enrolling 10,061 participants in the CANTOS trial. In the study, patients were randomised into four arms: placebo; 50 mg canakinumab; 150 mg canakinumab; and 300 mg canakinumab. All doses were given once every 3 months. Serum urate levels and high sensitivity C-reactive protein levels were initially measured and recorded at baseline and followed up every 3 months during the first year of the study. After the first year, measurements were taken annually. At baseline, gout status, determined by the physician's diagnosis, was recorded, and any subsequent gout recurrences were noted during follow-up as a section of the systematic adverse event reporting.

"Our results demonstrate a striking effect of canakinumab on reducing the risk of gout attacks in atherosclerosis patients"

In this secondary analysis, the researchers divided the participants from the original study into three groups determined by baseline serum urate level: <6.9 mg/dL (low), 6.9–8.9 mg/dL (medium), and ≥9.0 mg/dL (high). One aspect of the analysis involved investigating the potential of serum urate as a biomarker. A correlation between baseline serum urate with gout flare and major cardiovascular event rates was found. The rates of gout flares per 100-person years were found to be 0.28, 1.36, and 5.94 for the low, medium, and high baseline serum urate groups, respectively. It should be noted that canakinumab did not influence serum urate levels; this result was expected, due to canakinumab's mechanism of action.

A further aspect of the analysis was examining the impact of canakinumab on gout flare rates. The drug (in pooled doses) was found to significantly reduce gout flare rates across all baseline serum urate groups. Respective hazard ratios (95% confidence interval) for the low, medium, and high serum urate groups were 0.40 (0.22–0.73), 0.48 (0.31–0.74), and 0.45 (0.28–0.72), respectively. Prof Robert Landewé, Chairperson of the Scientific Committee, EULAR, commented: "These are significant results as they add to the evidence base demonstrating a potential preventative role for canakinumab in patients with gout."

Lenabasum: Promising Treatment for Diffuse Cutaneous Systemic Sclerosis

LENABASUM has shown promising clinical results with acceptable safety in an open-label extension (OLE) of a Phase II study for the treatment of diffuse cutaneous systemic sclerosis (dcSSc). A EULAR press release dated 13th June 2018 reported these promising results, which are made even more astounding by the rarity of dcSSc, which affects just one of every four of the 30 people per million population per year diagnosed with systemic sclerosis (SSc).[1]

Lenabasum is a selective cannabinoid receptor type 2 agonist shown to reduce inflammation and fibrosis in animal models of SSc, and activates resolution of the innate immune response in humans. The drug was shown to cause changes in gene expression consistent with the biological effects of lenabasum on pathways relevant to SSc in a Phase II trial.[2]

Those patients who completed the Phase II trial (n=36) were enrolled into the 1-year OLE to receive 20 mg twice daily. Analysing the 25 patients who competed the OLE, an improvement in ACR CRISS score of 56% was observed along with a reduction in modified Rodnan Skin Score, HAQ-DI, Physician Global Assessment, and 5-D Itch Questionnaire by 8.6, 0.14, 0.9, and 2.3, respectively.

"Our results are very encouraging and reinforce the positive findings from the double-blind placebo-controlled part of the study with regard to safety and tolerability"

Mean duration of OLE treatment was 45 weeks, and 19 patients completed 60 weeks of treatment; three patients discontinued treatment, two due to adverse events (AE) and one withdrew consent. AE were reported in 33 of the 36 subjects, but only 7 were related to lenabasum, none of which were severe. Overall, 1 patient had AE considered life threatening, 3 patients had severe AE, 21 individuals had moderate AE, and 8 were mild. The most common AE from all subjects were upper respiratory tract infections (22%), urinary tract infections (14%), diarrhoea (11%), skin ulcers (11%), and mild intermediate dizziness (8%).[3]

"Our results are very encouraging and reinforce the positive findings from the double-blind placebo-controlled part of the study with regard to safety and tolerability," commented the principal investigator, Dr Robert Spiera, Director of the Scleroderma and Vasculitis Program, Hospital for Special Surgery, Weill Cornell Medical College, New York City, New York, USA. "We look forward to continuing our investigation to assess the role of lenabasum as a new treatment option for patients with dcSSc." To build on these promising results, an international Phase III clinical trial of lenabasum has begun and results are expected in the first half of 2020.[4]

References

1. Michigan Medicine. What is Scleroderma? Available at: http://www.med.umich.edu/scleroderma/patients/scleroderma.htm. Last accessed: 18 June 2018.
2. Spiera RF et al. A Phase 2 study of safety and efficacy of anabasum (JBT-101), a cannabinoid receptor type 2 agonist, in diffuse cutaneous systemic sclerosis. Abstract 2884. ACR Meeting, 7 November, 2017.
3. Spiera R et al. Safety and efficacy of lenabasum (JBT-101) in diffuse cutaneous systemic sclerosis subjects treated for one year in an open-label extension of trial JBT101-SSC-001. Abstract OP0006. EULAR 2018, 13–16 June, 2018.
4. Corbus Pharmaceuticals Inc. Trial to Evaluate Efficacy and Safety of Lenabasum in Diffuse Cutaneous Systemic Sclerosis (RESOLVE-1). NCT03398837. https://clinicaltrials.gov/ct2/show/NCT03398837.

Predicting and Preventing the Onset of Rheumatoid Arthritis

MOLECULAR changes that occur in rheumatoid arthritis (RA)-risk individuals could support development of early interventions to predict and prevent onset of the disease. As reported in a EULAR 2018 press release dated 13th June 2018, the results of two studies provide insights into gene signatures and biomarkers of arthritis onset that could inform novel diagnostics.

Focussing on RA-risk individuals who have specific RA autoantibodies but no evidence of joint destruction, the first study used synovial tissue of the knee joint and performed genome-wide transcriptional profile studies in 13 people. The resulting gene signatures were investigated using real-time PCR and showed that molecular changes appeared in the tissue before disease onset; a total of 3,151 transcripts were associated with a higher RA risk, including genes involved in several immune-response pathways. The analysis therefore successfully highlighted predictors of RA-risk individuals who will develop RA in the future, including positive glycoprotein 38 staining and lower lipid staining, enabling better understanding of the preclinical phase of the disease and suggesting novel drug intervention targets.

"These studies may help us better understand and potentially identify which individuals classified as at-risk will go on to develop RA"

The second study of individuals at risk of RA aimed to validate that B cell receptor (BCR) clones in the blood are a predictor of disease onset. According to the results, out of 129 participants, 45 had ≥5 dominant BCR clones, while the remaining were considered BCR-negative. After 104 months follow-up, 76% of the BCR-positive individuals developed RA compared to 13% of the BCR-negative cohort, equating to a relative risk of 5.8 (95% confidence interval: 3.2–10.3; p<0.0001). Further subanalyses showed that the number of dominant BCR clones significantly correlated with the risk of arthritis; for example, having ≥10 dominant BCR clones had a predictive value of 94% within 3 years. With a better predictive power compared to other available biomarkers, BCR clones could help clinicians predict imminent onset of RA in at-risk patients.

Since the structural joint damage associated with RA is irreversible, early recognition and treatment is vital to control disease progression. "These studies may help us better understand and potentially identify which individuals classified as at-risk will go on to develop RA," commented Prof Robert Landewé, University of Amsterdam, Amsterdam, Netherlands. He added: "This is important because it will contribute to the development of early preventative strategies, including potential pharmacological treatment to prevent onset of disease."

Significant Drop in Number of Joint Replacements

A DRAMATIC fall in the number of joint replacement procedures taking place in rheumatoid arthritis (RA) patients was highlighted by the results of a study reported in a EULAR press release, dated 13th June 2018. While the current scientific literature provides inconsistent evidence on the subject, one of the study authors, Dr John Hanly, Professor of Medicine (Rheumatology) and Pathology, Dalhousie University, Halifax, Canada, declared: "However, our results add significant evidence to show a clear reduction in joint replacement surgery in RA patients, most likely due to improvements in medical management over the last few decades."

The researchers conducted a retrospective cohort study. Healthcare administration data from 1997–2010 was used to match patients with RA by age and sex to randomly selected controls in a 1:4 ratio. Over the course of the study, the mean age of individuals in the cohort increased from 56.7 to 60.1 years. Furthermore, the proportion of females increased from 70.8% to 73.9%.

"...our results add significant evidence to show a clear reduction in joint replacement surgery in RA patients..."

Overall, there was a 51.9% reduction in the number of joint replacement surgeries in patients with RA surgeries over the study period. It was noted that, by comparison, the number of joint replacements in the matched control group increased by 31.9% (p=0.002) during the same time period; however, the number remained less than that seen in the RA patient group. The researchers also examined the rates of cardiac interventions in an attempt to discern whether changes observed in joint replacement surgery were as a result of access to surgical procedures or improvements in RA therapy. It was found that rates of cardiac interventions did not show a significant change in either study group across the time period, suggesting the latter explanation.

This finding represented exciting news for rheumatologists, with Prof Robert Landewé, Chairperson of the Scientific Programme Committee, EULAR, proclaiming: "We welcome these results demonstrating such a dramatic reduction of joint replacements in RA patients in recent years."

Cardiovascular Risk Linked to Pain Management Drug for Osteoarthritis

CARDIOVASCULAR risk in osteoarthritis (OA) patients has been linked to the cornerstone of OA pain management: nonsteroidal anti-inflammatory drugs (NSAID). Recent research has suggested OA is an independent risk factor for cardiovascular disease (CVD) and, according to a EULAR press release dated 13th June 2018, over two-thirds of the increased cardiovascular risk associated with OS is linked to NSAID use.

This pioneering longitudinal study evaluated the role of NSAID use in the development of CVD in 7,743 OA patients. Results showed OA patients had a 23% higher risk of developing CVD; the risk of congestive heart failure, ischaemic heart disease, and stroke all increased by 42%, 17%, 14%, respectively, in OA patients compared to the study's 23,229 non-OA controls matched for age and sex. Researchers then assessed these results in relation to NSAID use: 68% of the total effect of OA on CVD risk was caused by NSAID. Congestive heart failure risk due to NSAID was 45% and >90% for ischaemic heart disease and stroke.

"Our results indicate that OA is an independent risk factor for CVD and suggests a substantial proportion of the increased risk is due to the use of NSAID."

Prof Thomas Dörner, Chairperson of the Abstract Selection Committee, EULAR, explained why the link between cardiovascular risk and OA is an important area of study: "The examination

of cardiovascular risk among individuals with osteoarthritis is an important area of research as very little is known about the association, despite OA being the most common rheumatic disease with high prevalence among the elderly."

Study author Prof Aslam Anis, School of Population and Public Health, University of British Columbia, Vancouver, Canada, summarised the study results: "Our results indicate that OA is an independent risk factor for CVD and suggests a substantial proportion of the increased risk is due to the use of NSAID. This is highly relevant because NSAID are some of the most commonly used drugs to manage pain in patients with OA."

This study provides new information about the potential causal role NSAID play in the increased cardiovascular complications seen among individuals with OA. With these results there is no doubt that there needs to be further investigation into the effect that the widely prescribed NSAID can have on the cardiovascular health of OA patients.

The Youth-R-Coach Programme

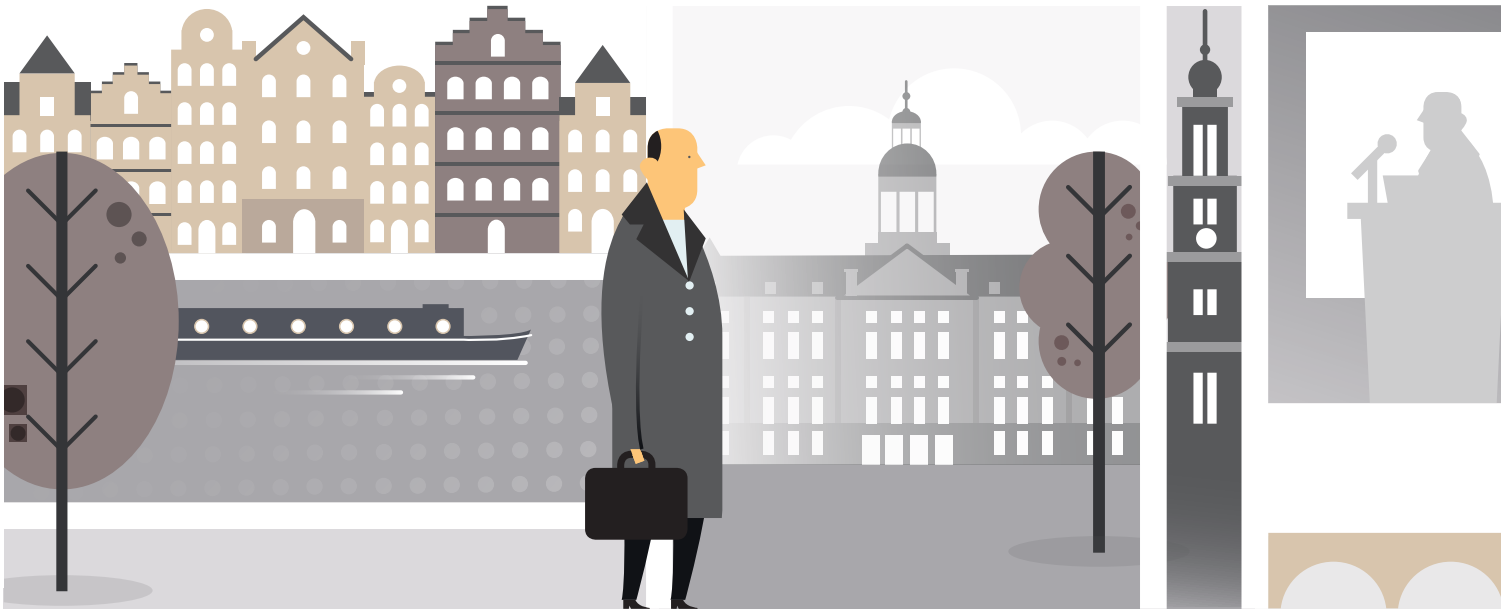
EMPOWERING young people to become 'experts-by-experience', the Youth-R-Coach programme enables young people with chronic disease to share their personal experiences and support their peers. The details of this peer-to-peer programme were presented at the EULAR 2018 Congress and described in a EULAR press release dated 14th June 2018.

With the aim of increasing awareness of the millions of young people living with chronic rheumatic and musculoskeletal diseases across Europe, the Dutch project works with young people aged 18–27 years to create self-written books based on their own personal experiences. The work ranges from short columns to entire novels and is aimed at other young people, family members, teachers, and healthcare professionals to provide valuable insights into living with a chronic illness.

The programme involves groups of seven young people who take part in a kick-off meeting, a training weekend, and a final group workshop to share online coaching and presenting skills; however, the writing process is very much based on the individual person. To further provide participants with new coping tools and skills to teach others about the disease, each person is also given a mentor with a similar condition, with whom they communicate throughout the writing process.

"We have been amazed by the energy and enthusiasm of all the participants to share their experiences and act as a coach to their peers."

Describing the great success of the project, Linda van Nieuwkoop, programme advisor and mentor for the Youth-R-Coach programme of Centrum Chronisch Ziek en Werk, Eindhoven, Netherlands, commented: "We have been amazed by the energy and enthusiasm of all the participants to share their experiences and act as a coach to their peers." She added: "We are delighted with the diverse range of books that we hope will support other young people coping with a rheumatic or musculoskeletal disease, as well as other chronic conditions."



This initiative supports Young PARE, a working group of the Standing Committee of PARE and part of EULAR, which works to establish and strengthen rheumatic and musculoskeletal disease youth groups across Europe and encourage the exchange of best practises throughout this network. Petra Balážová, Chair of Young PARE, expressed hope for international collaboration in the future following this initiative: "We hope that this will inspire other similar projects in other parts of the world."

Continued Developments in the Use of Methotrexate

METHOTREXATE (MTX) was first approved for the treatment of rheumatoid arthritis (RA) 30 years ago. Since that approval, MTX has become established as the gold standard. During this time period, research on MTX has not stood still. A large number of new findings and developments have been presented over the years, enabling MTX therapy to become increasingly optimised. These new developments combined with therapeutic MTX optimisation were the subject of a symposium at the EULAR Congress, reported in a EULAR press release, dated 15th June 2018.

One way in which MTX therapy has been optimised is in regard to dosage and administration; it has been reported that higher doses of MTX and subcutaneous administration are more effective than the tablet form. Additionally, further studies have refined the subcutaneous administration method. As a result of its simpler handling, RA patients have been shown to prefer the Medac autoinjector over the pre-filled syringe. Such a finding is important, as utilisation of a preferred application method can have a major influence on patient compliance with therapy.

Throughout the course of the event, the benefits of continuing research into RA therapeutic options were emphasised.

MTX is also being examined from a gastroenterological perspective: through the prism of the microbiome. It is known that the expression of rheumatoid arthritis, and potentially the disease's course, is influenced by the interaction between predisposed genetic factors and the microbiome. The influence of the microbiome on MTX is a topic of study. One piece of ongoing research has demonstrated that MTX has an inhibitory effect on the growth of different intestinal bacteria. Additionally, it is thought that the fact some species of bacteria can convert MTX into polyglutamated MTX might exert an influence on the efficacy of MTX therapy.

The symposium held at EULAR 2018 covered a variety of other topics, including MTX's position in the treatment of juvenile idiopathic arthritis and MTX combination therapy. Throughout the course of the event, the benefits of continuing research into RA therapeutic options were emphasised.

Congress Feature

Dr Louise Bennett

Rheumatosphere, University of Glasgow, Glasgow, UK

Building on last year's launch, the EULAR 'Don't Delay, Connect Today' campaign was a highlight of this year's EULAR Congress. As part of EMJ's independent review of the event, Dr Louise Bennett, a member of Rheumatosphere based at the University of Glasgow, Glasgow, UK, has kindly provided the following insights into how she and her colleagues took the campaign to some of Scotland's most remote areas.

Don't Delay, Connect Today: Scotland

Last year, the European League Against Rheumatism (EULAR) encouraged groups to apply for funding in order to implement their public engagement campaign 'Don't Delay, Connect Today' (DDCT) in their home country. The DDCT campaign aims to raise awareness about the importance of early diagnosis in the treatment of musculoskeletal (MSK) conditions, such as rheumatoid arthritis. By treating early in the well-established 'window of opportunity', patients have been shown to display better clinical outcomes in response to therapy. To this end, the campaign's focus is on equipping the general public with the information required to recognise the early warning signs of MSK conditions and, upon recognition, encourage them to connect with their local general practitioners (GP). In order to ensure that practitioners escalate these cases appropriately, campaigners will work with them to ensure that they recognise characteristic early warning signs and understand the importance of referring individuals to rheumatology specialists as quickly as possible.

Rheumatosphere, based at the University of Glasgow, Glasgow, UK, was awarded funding from EULAR to implement the DDCT campaign in Scotland, and we decided to take our work to some of the country's most remote areas: the Outer Hebridean islands. These islands currently have limited access to MSK disease specialists; hence, the campaign is aimed at providing the residents with the information they need to recognise early indicators of disease and raise their concerns with their GP. This will result in them receiving treatment earlier. In order to raise awareness, our team set out to hold six public engagement events across the islands, thereby interacting with as many individuals as possible to have the greatest impact with the campaign. Events were held in North Uist, Leverburgh, Tarbert, Callanish, and Stornoway, with the largest event taking place at the Callanish Standing Stones visitor centre and the local Co-operative supermarket. At the visitor centre, we were able to engage with both

locals from the islands and the tourists who come to visit, often on bus tours, hence increasing the amount of interaction we had. Engagement at the Co-operative supermarket was also very productive due to footfall; here, we engaged with hundreds of local residents, giving out flyers about the campaign and also talking to those who had already received a MSK disease diagnosis.

Throughout the campaign, we have endeavoured to raise awareness through social media; Rheumatosphere has a presence on Twitter, Instagram, and Facebook to reach as wide a demographic as possible. Twitter analytics showed that during the month of our cycle event, we had 1,188 Twitter page visits, 29 new followers, and an astonishing 20,300 Twitter impressions. Further to this, a Facebook video was posted on the Callanish Standing Stones centre page, informing the public of who we were and what we were doing at the visitor centre. This video managed to gain an impressive 638 views. Through social media, we were able to extend the impact of our events, greatly increasing the number of individuals who saw the essential messages of the DDCT campaign.

"These islands currently have limited access to MSK disease specialists; hence, the campaign is aimed at providing the residents with the information they need to recognise early indicators of disease and raise their concerns with their GP."

As previously stated, there is limited access to rheumatology and MSK services on the Outer Hebridean islands; rheumatology education for primary healthcare professionals (HCP), including GP, nurses, and physiotherapists, is therefore an essential tool. Capitalising on this, we ran an event for all primary HCP through which we were able to reinforce the early warning signs of MSK conditions and highlight when individuals should be referred to rheumatology services. Since there is only one visiting rheumatologist and one permanent rheumatology nurse in this area, we also wanted to avoid overloading their system with unnecessary referrals, making this training and guidance for primary HCP all the more impactful and essential on the islands. Our HCP event was well attended and we were able to inform the attendees about the campaign and discuss at length ways in which the HCP on the islands could work together to improve care and treatment of MSK patients.

One of Rheumatosphere's aims, along with its partner organisation for the DDCT campaign, the National Rheumatoid Arthritis Society (NRAS), was to engage with those on the islands already living with MSK conditions. NRAS provided excellent marketing support for the event, along with educational materials for those patients on the islands already living with disease. With an NRAS ambassador who accompanied the Rheumatosphere team to the islands, we were able to hold two patient meetings: one on the Isle of Harris and another on the Isle of Lewis.

"This expedition was exciting and often challenging for the team; it involved cycling through wind and rain (and on occasion sunshine), riding against the clock to make connecting ferries, and ascending >600 foot to conquer the Clisham in Harris before reaching the final destination."

Further to the engagement work carried out on the islands, seven members of the Rheumatosphere team also cycled the Hebridean Way from Vatersay to the Butt of Lewis, raising money for NRAS. Our challenge was endorsed by Mark Beaumont, who launched the Hebridean cycle in 2016, cycling the 185 miles in under 24 hours. Mark stated: "I am delighted to add my support to a team of clinicians and scientists from my alma mater, the University of Glasgow, who are taking on the beautiful Hebridean Way cycle challenge. Setting out on 13th May, this 185-mile route traverses the length of the Outer Hebrides and is in support for EULAR and a campaign called 'Don't Delay, Connect Today'."

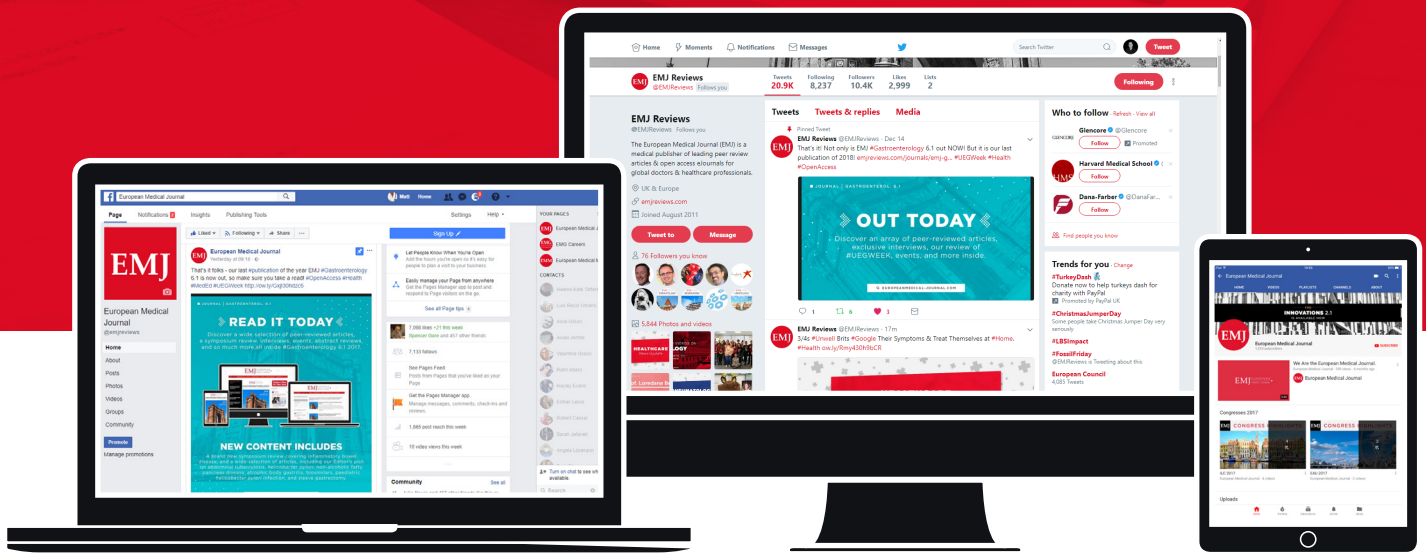
The team completed the 185-mile cycle in 4 stages: the first was 65 miles from Vatersay to North Uist, the second was 50 miles from North Uist to Tarbert, the third was 40 miles from Tarbert to Gearrannan, and the fourth was 30 miles from Gearrannan to the Butt of Lewis lighthouse. This expedition was exciting and often challenging for the team; it involved cycling through wind and rain (and on occasion sunshine), riding against the clock to make connecting ferries, and ascending >600 foot to conquer the Clisham in Harris before reaching the final destination. Having been successful in completing our cycle, we were able to raise >£3,000 for NRAS.

The Rheumatosphere team, along with NRAS, has taken on the challenge of delivering the DDCT campaign and enjoyed every minute of it; we are now planning to extend the campaign's reach through more of the Scottish islands. I would encourage anyone interested to get involved in this worthwhile cause; take a look at the EULAR website for more details of the campaign:

https://www.eular.org/what_we_do_dont_delay_connect_today_2018.cfm?fromSearch=don%27t%20delay

"The Rheumatosphere team, along with NRAS, has taken on the challenge of delivering the DDCT campaign and enjoyed every minute of it..."

Interact with us on social media.



Join the European Medical Journal community and discover news on the latest healthcare developments.

EUROPEANMEDICAL-JOURNAL.COM

Interviews

Insightful interviews from members of the *EMJ Rheumatology* Editorial Board, including the esteemed Editor-in-Chief Dr Ian C. Chikanza

Featuring: Dr Ian C. Chikanza, Dr Christakis Christodoulou, and Prof Prodromos Sidiropoulos

Dr Ian C. Chikanza

Barts and the Royal London Hospital, UK

You have credited your parents with encouraging you to pursue a medical career. Can you tell us about your early medical education and how important it was to have a positive support network during your training?

Medical school studies are very demanding; you have to read a lot and do lots of practical clinical work. Therefore, having a supportive family is vital for success. I was grateful that both my parents and maternal grandmother were around (now my father and grandmother have since passed) and their never-ending support and encouragement were instrumental in my success. As a medical student, I also got a lot of support, mentorship, and encouragement from Dr Ben Mbengeranwa, the late Dr Clever Mamvura, Prof Kusum Nathoo, Dr Richard Laing, and Dr James Kutshwa. During my pre-Membership of the Royal College of Physicians (MRCP) years, Prof Jimmy Thomas, Prof Charles Olweny, Dr Nelson Okwanga, Dr Robin Stott, and Mr Mauchaza supported me. Prof Olweny encouraged me to do research and to embark on an MD degree on typhoid fever early in my career. Dr Mbengeranwa, Prof Thomas, and Prof Olweny shepherded me on this work, and I was able to publish three papers on typhoid fever and another three (six in total) by the second year of being medically qualified. Prof Rodney Grahame was instrumental in getting me to specialise in rheumatology. He has been, and continues to be, my mentor and hero and has played a big part in ensuring my success in both internal medicine and rheumatology internationally, including in the UK and USA. I must also not forget to mention Dr Luke Fernandes and Dr Michael Wright, whose support and guidance were also phenomenal in shaping my career. Finally, I continue to acknowledge the enduring and unending support I continue to receive from my family who also put up with my many scientific brainwaves.

What treatment or technology, in your opinion, has had the greatest impact on the field of rheumatology in your lifetime?

The understanding of the molecular basis of inflammation, concepts of proinflammatory and anti-inflammatory cytokines, the role of neuroendocrine regulation in chronic autoinflammatory disease, corticosteroid resistance (which also has implications for determining responsiveness to anti-tumour necrosis factor [TNF] biodrugs), and monoclonal antibody production technologies, such as phage display array technology, have really advanced the field of rheumatology, especially disease management. The latter has also benefitted the management of other chronic autoimmune inflammatory conditions, such as inflammatory bowel disease. The use of more targeted approaches to managing inflammation, early diagnosis of rheumatic and musculoskeletal diseases (RMD), and early treatment, plus the concept of treat-to-target, with the target being switching off inflammation, has led to improved disease management outcomes that are benefitting patients with rheumatic disorders. Targeted approaches, such as anti-TNF biodrugs (biologics, e.g., adalimumab, etanercept, and enbrel), anti-interleukin (IL)-6 strategies (tocilizumab, sarilumab, sirukumab, clazakizumab, gerilimzumab, vobarilizumab, and novimmune), and anti-IL-1 drugs (anakinra [IL-1 receptor antagonist], canakinumab, rilonacept) have been highly successful in the management of a number of inflammatory disorders; these include rheumatoid arthritis (RA), axial spondyloarthritis, psoriasis and psoriatic arthritis, Behçet's disease, Still's disease (adult and paediatric), juvenile idiopathic arthritis, and inflammatory bowel disease. Abatacept targets and modulates the interactions between T cells and macrophages. Targeting the IL-23 and IL-17 cytokine pathway (ustekinumab [anti-common p40 subunit of IL-12 and IL-23] and secukinumab [anti-IL-17]) has had a great impact on the therapy of psoriasis and psoriatic arthritis, while targeting B cells with biodrugs such as rituximab, belimumab, atacicept, ofatumumab, and tabalumab has revolutionised the management of systemic lupus erythematosus (SLE) and RA, including vasculitis. Other inflammatory conditions beyond rheumatology have also benefited from these huge strides in medical innovation. Unfortunately, these therapeutic approaches are very expensive and are unaffordable in most developing countries. The recent development of biosimilar biodrugs that are considerably cheaper than originator drugs will go a long way to address the cost issues associated with biologic drugs.

Targeted chemical drug development has now caught up with the targeted biologic innovation. The targeting of specific intracellular signalling pathways, such the JAK kinase pathways, has been successful. Tofacitinib (Pfizer, New York City, New York, USA) and baricitinib (Eli Lilly, Indianapolis, Indiana, USA) are now in clinical use, whereas others are in clinical development. One would have expected these oral chemicals to be cheaper than biodrugs; however, at present the pharmaceutical companies are unfortunately charging prices similar to that of originator biodrugs, making this technological leap in medical care out of reach for a very large percentage of humanity suffering from inflammatory RMD around the world.

"The recent development of biosimilar biodrugs that are considerably cheaper than originator drugs will go a long way to address the cost issues associated with biologic drugs."

Imaging technologies, such as magnetic resonance imaging (MRI) scanning and nuclear medicine fluorodeoxyglucose positron emission tomography scanning, are now enabling us to detect inflammation in ways that have never been seen before, including vasculitis. Techniques to quantify inflammation with dynamic MRI are being developed. This will fast-track new drug evaluations in inflammatory disorders. The introduction of dual-energy computerised tomography (CT), which characterises the chemical composition of material according to its differential X-ray attenuation at two different energy levels, is another revolutionary addition to musculoskeletal imaging. Dual-energy CT can image bone marrow oedema, tendons, and ligaments, with the most validated application being the highly specific ability to detect monosodium urate deposits in the assessment of gout.

Your research into neuroendocrine immunology of inflammatory arthritis has been revolutionary, and the work contributed to the development of biodrugs that are now being used for a wide variety of chronic inflammatory conditions, including Crohn's disease and ulcerative colitis. When you first began working on this topic, did you predict that the results would have such widespread applicability?

When I started pioneering work on the neuroendocrine immune regulation of inflammation in RA (Dr Ron Wilder and Dr George Chrousos at the National Institutes of Health [NIH] had done a lot of pioneering work in Lewis and Fischer rat animal models of inflammation), I had no idea that this work would unravel such an understanding of the inflammatory processes in humans in such an explosive way. The work in RA not only revealed defective neuroendocrine immune responses to systemic inflammation but also that the production of natural anti-inflammatory factors such as IL-1 receptor antagonist and soluble TNF p75 and p55 receptor shedding were deficient and/or dysregulated. We still do not know whether these observations are a consequence of deficient cortisol and upregulated prolactin secretion in RA inflammation; however, combined, these observations led firstly to the concept of the neuroendocrine immune loop with positive and negative feedback regulation and that, if it was defective, as observed in RA, SLE, and juvenile idiopathic arthritis, it could contribute to the development of chronic autoimmune inflammatory disease. Secondly, the need for a finely tuned appropriate balance between proinflammatory and anti-inflammatory factors is essential in the control and switch-off of inflammation and the subsequent restoration of the physiologic *status quo ante*. The latter could be achieved using monoclonal antibodies to neutralise proinflammatory cytokines or by using recombinant proteins (based on the naturally occurring inflammatory inhibitors), and this switch-off has had important therapeutic implications. The therapeutic applications of anti-TNF biodrugs, anti-IL-6 strategies, and anti-IL-1 drugs have been highly successful in the management of a number of inflammatory disorders, such as RA, axial spondyloarthritis, psoriasis and psoriatic arthritis, Behçet's disease, Still's disease (adult and paediatric), juvenile idiopathic arthritis, and inflammatory bowel disease. This trend of thinking has also influenced the development of other targeted approaches on the IL-12/IL-23/IL-17 pathways, as previously discussed.

"Medical school studies are very demanding; you have to read a lot and do lots of practical clinical work. Therefore, having a supportive family is vital for success."

As a specialist in both adult and paediatric rheumatology, what do you consider to be the most important difference in treating these two patient groups?

There are many fundamental differences in these two rheumatic patient groups. The paediatric group is further subdivided into children and adolescents, and there are actually two patients to deal with, so to speak. The first is the affected child and the second is the parent. Both need to be intimately involved in the management plans; however, even in adults it is important also to involve close relatives in treatment plans. The main focus should always be the needs of the patient and offering the best care at any given time.

How important is interdisciplinary co-operation for the successful treatment of rheumatology patients?

Rheumatology, in my view, now forms a large part of medical care. Inflammatory rheumatic diseases affect the pulmonary, cardiac, renal, vascular, and ophthalmic systems, and are a risk factor for neoplasia. The core healthcare professionals in rheumatology care and rehabilitation of rheumatic disorders have traditionally been the rheumatologist, rheumatology nurse, and physiotherapist. In my view, given the wider systemic nature of rheumatologic disorders, it is very important now to expand this core team to include other professionals from other medical and surgical

specialities and to have multidisciplinary combined clinics to offer effective comprehensive rheumatologic care. In my hospital we have therefore combined clinics with nephrologists, cardiologists, and respiratory physicians. We also hold combined multidisciplinary meetings with orthopaedic surgeons.

"Other inflammatory conditions beyond rheumatology have also benefited from these huge strides in medical innovation."

Your impressive medical career spans three continents: Africa, Europe, and North America. How have your experiences in these diverse environments shaped your approach to rheumatological medicine?

This has been invaluable indeed. There are ethnic differences in the expression of rheumatic diseases and therapy responses. Environmental factors may also be at play. We have published work on RA regarding the ethnic and genetic differences in the disease expression in black African and Caucasian patients in the UK and Zimbabwe. Currently, with my colleagues in Zambia, Dr Njobvu and Dr Trollip, we are also looking at the ethnic differences in the expression of SLE and scleroderma in patients from Zimbabwe, Zambia, and the UK. A full understanding of these differences, in our opinion, will contribute to the development of personalised rheumatologic care. Another important aspect is also the differences in the level of funding available for the care of rheumatologic patients, which varies significantly across the globe. It is therefore important to develop treatment protocols that are suited to the country that one is practising in. One of the areas that myself, Dr Trollip, and Dr Njobvu are working on is to refine the treatment algorithms developed by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) so that they can best be tuned to suit the medical conditions of a local country. This aspect is funded in part by the International League Against Rheumatism (ILAR) and ACR grants awarded to us.

You were born in Zimbabwe and much of your work still takes place there. What challenges do rheumatologists currently face in Zimbabwe, as well as in Africa as a whole?

The first challenge is the lack of rheumatologic expertise in Zimbabwe and in most African countries. Many patients are diagnosed late and the treatment they get is not optimal. In addition, funding for treatments and even blood test monitoring is a major challenge. Patient education and public awareness, as well as medical community awareness of the need for proper early diagnosis and treatment, of RMD are lacking. RMD are an unmet medical need in Zimbabwe and the rest of Africa. There are also serious drug and general medical manpower shortages that severely impact RMD diagnosis and management. We are tackling this challenge head-on in the 15 Southern African Development Community (SADC) states. To raise public and government awareness of RMD, together with my colleagues Dr Njobvu, Dr Trollip, and Prof Adelowo, President of the African League Against Rheumatism (AFLAR), I intend to host the first World Arthritis Day (WAD) Africa Conference in Victoria Falls, Zimbabwe around the anniversary of WAD on 12th October, which is to be attended by healthcare professionals and government officials from all African states. The aim is to raise awareness of RMD, the need for early diagnosis, and early effective appropriate treatment in order to prevent development of RMD complications, comorbidities, and loss of the economic capacity of affected individuals. RMD also increase the risk of developing cancers such as lymphomas, as well as others. We also intend to highlight the effect of RMD on worsening gender disparity in women, which also negatively impacts child welfare. In Africa, women are the economic backbone in many families. We are soliciting the World Health Organization (WHO), UNICEF, United Nations (UN), World Bank, International Monetary Fund (IMF), Department for International Development (DFID) UK, Save the Children UK and USA, and the Joint United Nations Programme on HIV/AIDS (UNAIDS) to join us in this endeavour. The government of Zimbabwe and Zambia will co-host this conference with the Arthritis Care Africa Foundation (ACAF). I therefore extend an

invitation in advance to all physicians, general practitioners, rheumatologists, allied healthcare professions, pharmaceutical industry members, among others, to this inaugural conference on RMD in Africa. Let us work to address this unmet medical need in Africa and make a difference. We hope that a number of companies will generously sponsor this conference and that it will become an annual event around the anniversary of the World Arthritis Day.

You also founded the Arthritis Care Centre in the Zimbabwean capital, Harare, which was funded by a grant from the ILAR and the ACR. How important is it for governments and medical professionals to collaborate with societies such as these to improve the availability and quality of care, especially in developing countries?

ILAR and ACR awarded me a grant to cover some of the costs for 1 year to set up the Arthritis Care Centre in Harare, with the aim of creating a rheumatology clinic to spearhead training for rheumatology nurses and doctors. The funding for medical services in Zimbabwe, like in other African states, is in dire straits. We started setting up the clinic at Parirenyatwa Hospital in Harare but the funds were not enough to even furnish the clinic and run it effectively. However, monthly teaching at medical grand ward rounds and monthly general practitioner meetings were started to raise awareness of RMD. This project is, however, in desperate need of funding to move it to the next stage. It is very important for governments and medical professionals to engage with such societies to improve RMD awareness, training, diagnosis, and management. What is important in Africa is for the WHO to take a prominent position on RMD as an unmet medical need area for support and aggressive development. I am working with my Zambian colleagues also to set up a similar Arthritis Care Centre model in Zambia. We strongly believe that by setting up such a network of Arthritis Care Centres in Africa offering standardised rheumatologic care and providing rapid access to rheumatology expertise using all available communication technologies, training of rheumatology nurses will rapidly address in part the unmet needs in RMD. We plan to use telemedical strategies to reach many patients with RMD in the 15 SADC states to start with.

You are deeply passionate about improving the quality and availability of rheumatological care in Africa. What inspired you to set up the ACAF and how does it aim to improve arthritis care across the continent?

There is no specific educational support for individuals living with arthritis in Africa and public awareness of RMD is poor. As a result, governments in Africa do not prioritise RMD even though the conditions lead to a large number of lost working days, negatively impacting economic development and child welfare. In Africa there is a lack of training in RMD for healthcare professionals and many patients cannot afford the treatments. In addition, there are very few rheumatologists in Africa. This spurred me, my colleagues, and some patients to set up the ACAF. The aim of the ACAF is to be an organisation dedicated to supporting people living with arthritis in Africa by raising funding to support initiatives geared to this objective. The ACAF is also a platform of knowledge-sharing for people living with arthritis in Africa and represents, as well as lobbies for, arthritis-related issues at local, regional, and global platforms, engaging in fundraising activities for research development as well as treatment. Some of its work will include supporting activities around WAD throughout Africa, working together with relevant bodies such as the WHO, among others. The trustees of the ACAF are people living with arthritis and include world-renowned experts in the field.

What advice do you have for young medical students looking to start a career in rheumatic medicine?

Foremost, they need to be very good in internal (general) medicine, as well as loving people and wanting them to be healthy and to feel good about themselves. More fundamentally, I encourage students to always put the interests of patients first and to always want to give them the same treatment they would like to receive if they were the patient.

Dr Christakis Christodoulou

University of Nicosia Medical School, Cyprus

What first inspired you to pursue a career in rheumatology?

During my 3-year Senior House Officer medical rotation at Southampton University Hospitals NHS trust, Southampton, UK, I had the opportunity towards the end of 1999 to work in the department of rheumatology for 4 months. I was fascinated by the complexity of the rheumatological conditions, the new revolutionary treatments that were on the horizon, the fact that in this speciality the treating rheumatologist can build up a long-standing working relationship with their patients due to the chronicity of rheumatological conditions, and I was very impressed by the excellent relationship between the doctors, nurses, physiotherapists, and occupational therapists that worked in the department. There was an excellent team spirit.

During your training, were there any formative moments that made you change your approach to medicine?

Medicine is very complex and evolves continuously. Several moments throughout my career made me realise the importance of paying attention to detail, since in medicine small details can sometimes make a huge difference to the outcome and whether or not a patient survives, e.g., too low or high potassium. Moreover, we deal with human beings and we have to respect them and listen to their worries and wishes; we need to make our patients partners in their treatment decisions.

Having spent a portion of your professional career in the UK, what do you consider to be the main differences between rheumatology practice in the UK and in your native country of Cyprus?

I was in the UK for 16 years, undergoing all my undergraduate and postgraduate training, which was time that I thoroughly enjoyed. I have been working in Cyprus since September 2007. The rheumatology practice in both countries is very similar in various aspects and is mainly outpatient based. Inflammatory arthritis seems to be more severe in a larger proportion of patients in the UK than in Cyprus. Moreover, we see Adamantiades-Behçet's disease and familial Mediterranean fever more commonly in Cyprus than we did in the UK. In the UK there are many more opportunities for research than Cyprus and in the UK you hear about new treatments some years before they become available in clinical practice.

Are there any rheumatological conditions that are particularly prevalent in Cyprus or the surrounding regions? What challenges do these conditions pose for rheumatologists and national policymakers?

Like the rest of Europe, the most prevalent rheumatological conditions are osteoarthritis and osteoporosis. There are 19 rheumatologists in Cyprus for a population of about 700,000 people and therefore we can easily cope with the number of patients. There is good collaboration between the public and private sector, which helps improve the management of our patients. As previously mentioned, Adamantiades-Behçet's disease and familial Mediterranean fever are more common in our region.

You served as the President of the Cyprus Rheumatology Society from January 2016–December 2017. What, in your opinion, were the most important achievements for the society during your presidency?

We organised three major successful rheumatological conferences during my term as president. We organised the 8th and 9th Crete-Cyprus rheumatology symposia; the 8th was in Herakleion, Greece, and the 9th in Limassol, Cyprus. These meetings were very successful and during the symposia we exchanged views

on a variety of practical issues in the day-to-day diagnosis and management of our patients.

During my presidency, we also organised the 2nd Rheumatology Day conference in collaboration with the societies of the general (internal) medicine physicians and general practitioners. The aim of this conference was to increase the awareness of rheumatological conditions, their presentations, diagnosis, management, and the need for early referral of patients with suspected inflammatory arthritis. Moreover, we significantly improved the public sector treatment protocols for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis and for the first time we included four new biologics: tocilizumab, rituximab, secukinumab, and ustekinumab. Approval from the responsible officer for the personal data protection for the launch of the Cypriot biologics register was also obtained by the society.

"Several moments throughout my career made me realise the importance of paying attention to detail, since in medicine small details can sometimes make a huge difference to the outcome and whether or not a patient survives..."

The society also had an active participation in EULAR and took part in two EULAR executive meetings. We significantly upgraded the Cyprus Rheumatology Society website and, in collaboration with Pfizer, we prepared a booklet on immunisations for our patients with rheumatological conditions.

You are contributing a poster to the XVII Mediterranean Congress of Rheumatology in Genova, Italy. Could you tell us a little more about this poster and, more broadly, about how nutrition and climate impact musculoskeletal diseases?

In the poster we present a young lady with an atypical presentation of rheumatoid arthritis and then review the literature on issues related to this atypical presentation. Rheumatologists need to be aware of atypical presentations of common diseases. Our patient, a 38-year-old female, presented with pain in the left temporomandibular joint of 1-year duration. She was diagnosed with rheumatoid arthritis and responded very well to treatment with a single injection of intramuscular depomedrone 120 mg and methotrexate. She also had physiotherapy on the temporomandibular joint.

Healthy nutrition and exercise contribute to the health of the musculoskeletal system by helping to maintain a normal weight and also the muscles in a good condition. As we all know, the muscles support our joints. Moreover, a healthy diet can help to maintain our uric acid levels to normal levels, which is very relevant to patients with gout.

Weather conditions are also important; cold weather, as we all know, can lead to flare up of Raynaud's phenomenon and can cause the development of finger ulcers. From my working experience in the UK, many patients with arthritis felt worse in the winter, especially during periods of cold and wet conditions. On the other hand, hot weather like we have in Cyprus during the summer can lead to flare ups in our patients with SLE. Therefore, we advise these patients to avoid sun exposure and to use sun block with a high protective factor up to every 4 hours.

Musculoskeletal ultrasound is a key technique for the diagnosis of a wide range of injuries and diseases. How have the technology and techniques involved with this form of imaging changed throughout your career?

I started training in rheumatology in April 2002. During my career, musculoskeletal ultrasound evolved gradually in the assessment of patients presenting with a variety of rheumatic diseases, including inflammatory arthritis and soft tissue rheumatism. Initially, it was used in clinical studies, but currently many rheumatologists around the world use it in their day-to-day clinical practice. It is of great help in the assessment of patients with early arthritis, especially in those cases where it is not clear cut if they have synovitis and how many joints are affected, and it is also of great help in the assessment of patients with tendonitis, e.g., of the rotator cuff

and of the Achilles tendon. Musculoskeletal ultrasound is gradually becoming the stethoscope of the rheumatologist.

What do you think will be the largest challenge faced by rheumatologists over the next decade?

I believe that the largest challenge to be faced by rheumatologists over the next decade will be the efforts to find a definitive cure for inflammatory arthritis. The better understanding of the pathophysiology of rheumatic diseases and the advent of new treatments raise further expectations that definitive cures can be a realistic goal. Moreover, the increasing age of the European population will lead to a further increase in common diseases, such as osteoarthritis and osteoporosis, and this will put further strain on rheumatology services in countries where there are not enough trained rheumatologists.

You are a prolific educator, teaching students both during your time in the UK and now in Cyprus. What qualities do you think are of the highest importance for a medical educator? And for a medical student?

Whatever we do in life, in order to be successful we have to love and enjoy it. A medical educator needs to have a good knowledge and understanding of each topic that he or she will teach, prepare well for the teaching session, explain it in a clear and simple way, and also try to make the session lively and interactive. They need to be approachable to the students and make them feel comfortable and welcome to ask any questions they may have. Medical students also need to be enthusiastic, and prepare well before the session but also revise it afterwards; they also need to interact with their trainer and ask any questions they may have.

Considering the ever-growing reliance on technology across all branches of medicine, how important is it for physicians to emphasise compassion and interaction with patients during clinical practice?

Compassion and interaction with patients are vital for a number of reasons. Particular importance needs to be paid in history-taking and clinical examination because at least 70% of the diagnosis can be obtained by these measures.

Technology and investigations can be used to confirm the diagnosis. If we have empathy and compassion and interact with our patients, then they are a lot more likely to trust us and follow their treatments correctly and therefore they will have a better prognosis. Patients with most rheumatic diseases have chronic conditions and therefore can build up a long-term working relationship with their rheumatologist, which is good for both the patient and the physician.

Prof Prodromos Sidiropoulos

University of Crete, Greece

What first inspired you to become a doctor and, more specifically, a rheumatologist?

Making choices about your future career during adolescence is a rather difficult but interesting procedure. For me, it was a really difficult choice since I was not the kind of person with a true 'love' for one scientific field; I had rather multiple interests. Nevertheless, what weighted the choice was the 'value' of the field that I was going to study. I consider biomedical sciences to always have a true value as one of the most interesting and promising fields. During my studies in medical school, I found immunology an interesting field, and the implication of immune mechanisms in human diseases and the diverse phenotypes of systemic autoimmune diseases

were the main reasons I chose rheumatology as my specialism.

What moment from your early training as a rheumatologist had the biggest impact on your career? Was there a point that changed your perspective on rheumatology, or on medicine more generally?

Before starting medical training in rheumatology, I had the opportunity to get involved in research in the field of autoimmunity and inflammation, and the head of my laboratory and the staff were all really inspiring! Working in an academic environment, with persons dedicated to their work and who were open to adopt and train young investigators, was really a great challenge for me. I am grateful to them for widening my horizons!

"Making choices about your future career during adolescence is a rather difficult but interesting procedure. For me, it was a really difficult choice since I was not the kind of person with a true 'love' for one scientific field..."

What does a typical day as Professor of Rheumatology at the University of Crete entail?

We usually start with clinical duties, including the morning report. This is central to the set-up of the working plan in the clinic but at the same time is the most important case-based educational activity for the fellows. Time dedicated to teaching pregraduate medical students is rather limited in the traditional way (lessons in an amphitheatre), but teaching by the bedside is now an important task for medical students; we perform this for 3–4 months per academic year. Besides clinical duties, working with the staff in the research laboratory is an everyday task and a really refreshing procedure. Thus, lab meetings for problem-solving in ongoing projects, discussions about future projects, and web-based meetings with collaborators are all in the weekly agenda. Of course, administrative work is another part of the game, although not the most interesting one!

As a teacher, what aspect of rheumatology do you find most difficult to teach students? How do you approach this when teaching to overcome this challenge?

Working with young students is challenging and difficult! The trickiest task is to attract their interest and get them involved in an interactive learning procedure. We have exceptionally clever students who have had different experiences and whom we have to approach in a 'clever' way. Case-based learning and a problem-solving approach is one interesting way to do this. Nevertheless, it is very important to emphasise that studying medicine is a full-time job; medical students need to be dedicated and invest seriously in their studies.

What do you find is the most rewarding part of teaching future doctors?

The challenge is to inspire young people in the field of biomedical studies. The reward will be to see the new generation of physicians being better at practising medicine and, if possible, being better personalities than we are.

Much of your research deals with disease pathogenesis, including work on inflammatory cytokines and innate and adaptive immune responses. What do you consider to have been the greatest advancement in rheumatic disease pathogenesis research in the last decade?

Concerning the field of inflammatory arthritides, the identification of inflammatory cytokines as key players in disease pathogenesis and the significant therapeutic effect of anticytokine therapies was a major advancement. Moreover, for the last 15 years, data from genome-wide association studies have confirmed several known and novel targets for rheumatoid arthritis pathogenesis. Novel research methodologies, including those

regarding gene expression and cell-specific gene expression and regulation, have revealed novel insights into the pathogenesis of complex diseases. The aim is to translate this knowledge into better diagnostic and prognostic tools and the introduction of more efficient treatments.

"Working in an academic environment, with persons dedicated to their work and who were open to adopt and train young investigators, was really a great challenge for me. I am grateful to them for widening my horizons!"

You recently published a paper on the genetics of juvenile idiopathic arthritis. What did the results of this study indicate about the importance of conducting comparative studies in different populations?

Genetic association studies are of importance to reveal novel molecules and pathways contributing to disease pathogenesis. Confirmation of the findings in different ethnic populations or in different inflammatory diseases consolidates the importance of the findings.

Departmental overlap is common throughout medicine; how important is a multidisciplinary approach for rheumatologists specifically?

A multidisciplinary approach is important both in the clinical and research fields. From the clinical perspective, given that systemic autoimmune diseases affect multiple organs, a multidisciplinary approach is mandatory in order to have optimal benefits for the patient. Concerning the research field, on the other hand, the immune system operates and contributes to the pathogenesis not only of autoimmune diseases but also in transplantation, oncology, and infectious diseases. Thus, cross-collaboration with these fields is important in order to advance our knowledge.

Could you tell us a little about your work with BeTheCure (BTCURE)?

Several European academic centres have been collaborating successfully together for the last 12–15 years within consortia supported financially by the European Union (EU). We contributed to BTCURE, together with several other European academic centres with an expertise in autoimmunity and inflammation. Scientifically, together with Dr Dimitrios Boumpas and Dr Panayotis Verginis, we investigated the cellular subpopulation of suppressive cells (myeloid-derived suppressor cells) and novel cellular mechanisms (NETosis) that may contribute to the pathogenesis of systemic lupus erythematosus (SLE). Collaborative work with centres of excellence is of major importance to accelerate scientific progress in the EU.

If you could cure one rheumatic disease, which would you choose and why?

I would choose SLE for two reasons:

1. There is an urgent unmet need for more targeted and effective treatments since the agents currently used are rather non-specific and have multiple side effects.
2. The mechanisms operating in SLE, if effectively regulated, could be a therapeutic target for other systemic autoimmune diseases with important unmet therapeutic needs.

VIEW MORE INTERVIEWS ONLINE ←

Anti-TNF in Rheumatic Diseases: Inventory and Outlook

This symposium took place on 14th June 2018, as part of the 19th European League Against Rheumatism (EULAR) Congress in Amsterdam, Netherlands

Chairperson: Peter Taylor[1]

Speakers: Jürgen Braun,[2] Paul Enck,[3] Glenn Haugeberg,[4] Raj Sengupta[5]

1. Norman Collisson Professor of Musculoskeletal Sciences, Botnar Research Centre; Department of Orthopedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK
2. Medical Director, Rheumazentrum Ruhrgebiet, Herne, Germany
3. Director of Research, Department of Internal Medicine VI: Psychosomatic Medicine, University Hospital Tübingen, Tübingen, Germany
4. Professor of Rheumatology, Norwegian University of Science and Technology, Trondheim; Head of Rheumatology Division, Department of Medicine, Hospital of Southern Norway Trust, Kristiansand, Norway
5. Consultant Rheumatologist, Royal National Hospital for Rheumatic Diseases, Bath, UK

Disclosure: Prof Taylor has received research grants, consultation, and/or speaker fees from Celgene, Eli Lilly, Janssen Pharmaceuticals Inc., Novartis, Pfizer Inc., UCB Pharma, Roche, GSK, AbbVie, Biogen, Galapagos, Sanofi, Sandoz, and Nordic Pharma. Prof Braun has received honoraria for talks, advisory boards, consultancies, and grants for studies from AbbVie (Abbott), Amgen, Biogen, BMS, Boehringer, Celgene, Celltrion, Centocor, Chugai, EBEWE Pharma, Epirus, Hexal, Hikma, Janssen, Medac, MSD (Schering-Plough), Mundipharma, Novartis, Pfizer Inc. (Wyeth, Hospira), Roche, Sanofi-Aventis, and UCB. Prof Enck has received an unrestricted grant from SymbioPharm and served as advisor for Allergan, Almirall, AstraZeneca, Bayer/Steigerwald, Biocodex, Boehringer Ingelheim, Ferring G.A., Heel, SymbioPharm, TEVA, and UCB; he has also received speaker honoraria from Almirall, Bayer/Steigerwald, Biogen, Boehringer Ingelheim, Chiesi, Heel, Sanofi, and SymbioPharm. Prof Haugeberg has participated in speaker's bureaus for AbbVie, BMS, Biogen, Amgen, GSK, Mundipharma, Takeda, Eli Lilly, Pfizer Inc., MSD, Novartis, Roche, and UCB; has received consultancy fees from AbbVie, Amgen, Pfizer Inc., Novartis, and Eli Lilly; has received grant/research support from Pfizer Inc. and Biogen; and is a major shareholder for DiaGraphIT AS. Dr Sengupta has received honoraria, expenses, and research grants from AbbVie, Celgene, MSD, Novartis, Pfizer Inc., UCB, and Biogen.

Acknowledgements: Writing assistance was provided by Laura Bella and Rugina Ali, Syneos Health, London, UK.

Support: Biogen provided funding for medical writing support for the development of this article. Biogen reviewed the article for medical accuracy and provided feedback to the authors. All named authors had full editorial control of the paper and provided their final approval of the content.

Citation: EMJ Rheumatol. 2018;5[1]:36-43.

Meeting Summary

With an increasing number of biosimilars receiving regulatory approval, the treatment landscape for rheumatic diseases is evolving. Healthcare professionals (HCP) are being presented with an expanding armamentarium of treatment options that can increase patient access to effective biologic therapies and offer an opportunity for healthcare systems to benefit from significant cost savings. In recent years, accumulation of clinical and real-world data with biosimilars has helped physicians gain confidence in the use of biosimilars in daily clinical practice. However, further information regarding best practices of how to effectively introduce biosimilar therapies into a busy clinic is still required. This symposium aimed to uncover various aspects of preparing for a switch, providing suggestions for clinical parameters and imaging tools to aid identification of patients who will respond optimally to biologic treatment. Additionally, HCP–patient communication was analysed from a psychosocial perspective, covering shared decision-making and how to appropriately address common concerns raised by patients. Finally, during this interactive session, country-specific perspectives on best practices for successful switching and the use of remote monitoring tools for patient follow-up were also discussed.

Introduction: The Treatment Landscape of Rheumatic Diseases

Anti-TNF therapies have revolutionised the treatment of rheumatoid arthritis (RA) and a number of other inflammatory diseases, including psoriatic arthritis, juvenile arthritis, Crohn's colitis, axial spondyloarthritis (axSpA) including ankylosing spondylitis, and psoriasis. However, the high cost of these agents has placed a significant burden on healthcare systems around the world. Between the first anti-TNF biosimilar receiving approval in 2013 and the anticipated arrival of adalimumab biosimilars from late 2018, the numerous biosimilars currently licensed in Europe have presented HCP with an opportunity to increase patient access to effective biologic treatments in a cost-effective manner. "The emergence of a large number of biosimilars in the past few years, namely for rituximab, infliximab, and etanercept reference products, has led to significant health-economic benefits, with savings estimated to be between €12 billion and €33 billion globally between 2007 and 2020.[1] Switching patients to biosimilars creates opportunities for very significant savings in the clinic, which can then be reinvested to benefit patients further," highlighted Prof Taylor.

The increasing level of clinical, registry, and real-world evidence has reinforced confidence in the effectiveness and safety of biosimilars, leading European regulatory authorities and drug associations to endorse the interchangeability between biosimilars and reference biologics. However, despite their confidence in initiating biologic-naïve patients, HCP remain unsure about the practical aspects of switching their patients from a reference biologic to a biosimilar: which patient should be switched, when, and how? Are there ways to select patients that will benefit from biosimilar treatment? How should a switch be communicated to a patient? Following a successful switch, is there a way to monitor the patient without burdening the practice or the patient? To help address these questions, the expert faculty and the audience discussed key considerations when switching patients to a biosimilar treatment, as well as follow-up methods currently available to help optimise patient management and ensure maximum treatment outcomes.

Identifying Patients Who Will Benefit Most from Biologic Treatment

Switching should not be perceived as a burden when considering a patient for biologic therapy; instead, this is a prime occasion to reassess the clinical and psychosocial status of a patient. Together, these assessments can help identify patients who will benefit the most from biologic therapy and help HCP prepare patients for a change in therapy.

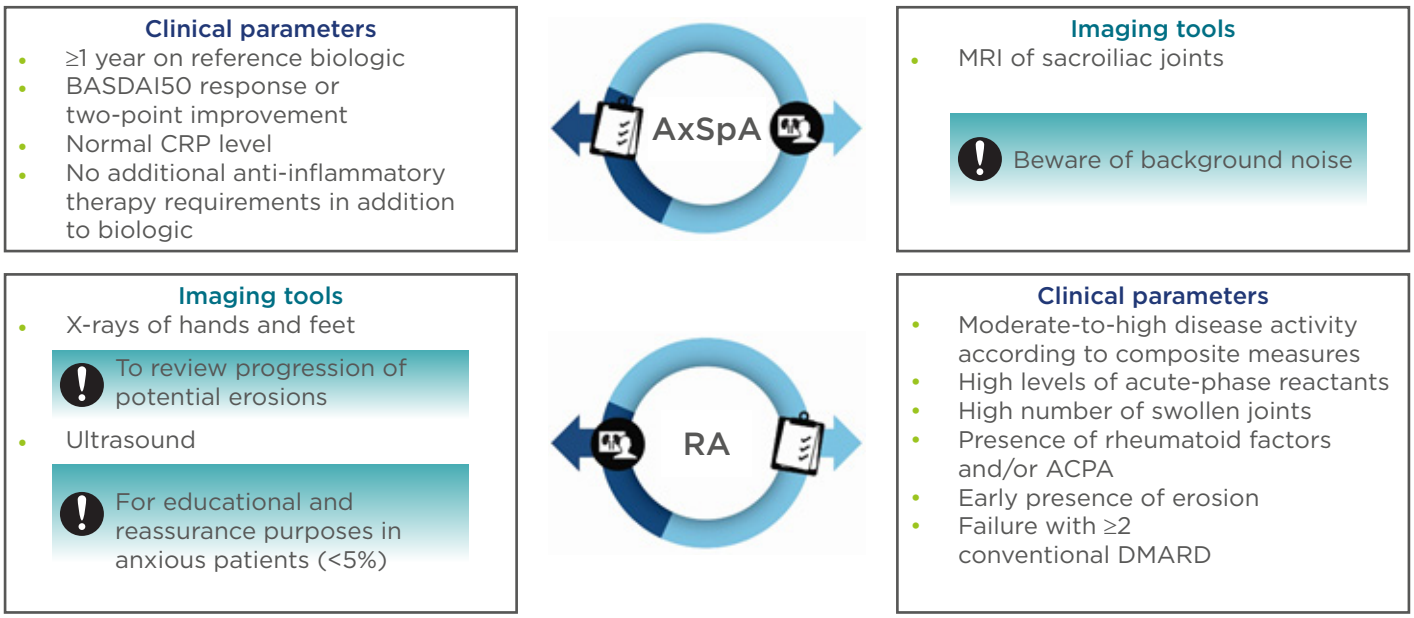


Figure 1: Clinical parameters and imaging tools to guide selection of patients with rheumatoid arthritis and axial spondyloarthritis for a switch to a biosimilar.

ACPA: anticitrullinated protein antibody; AxSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis.

Similarly, these evaluations can be applied to support patients switching from a reference biologic to a biosimilar to ensure that they experience an optimal response to the biosimilar. Here, Dr Sengupta and Prof Braun provided insights into which clinical and imaging criteria they consider when assessing patients with RA or axSpA for a switch to a biosimilar. Dr Sengupta highlighted: "Picking the right patient is possible and can bear real fruit, as most patients continue on the biosimilar when they are responding clinically."

When considering patients with axSpA, Dr Sengupta believes that it is important to select patients who are doing well on a reference biologic. The key clinical parameters used by Dr Sengupta can be found in Figure 1. In addition, he advised prudence when considering a switch for patients who are planning pregnancy or surgery, or for those who present with concurrent fibromyalgia.

Concerning imaging techniques, Prof Braun cautioned that in all patients with chronic inflammatory rheumatic diseases, such as axSpA, it is important to use imaging techniques (such as MRI) correctly to accurately define disease activity and help identify patients who are responding well to the reference biologic. With the occurrence of severe sacroiliitis, presenting with a large bone marrow oedema on MRI, and human leukocyte antigen-B27 being predictive of the development of ankylosing spondylitis, Prof Braun advised that there is value in obtaining an MRI of the sacroiliac joints. This can be used not only for diagnosis or classification but also for the assessment of disease activity at baseline and follow-up, as well as for prognostic purposes. However, it is important to correctly interpret the MRI changes because it is known that at least some of the changes may also occur in healthy individuals.[2-4] "Reference biologics, such as anti-TNF therapy, have been shown to be effective in targeting inflammation, whether in the sacroiliac joints, the spine, or the peripheral joints such as the knee. Within 6–12 months, the inflammation is usually cleared,[5] but in up to 20% of cases, a follow-up MRI may reveal some residual inflammation. The significance of this finding is, however, unclear, especially

as the correlation to the clinical finding is reportedly marginal.[5] Since no studies have been performed in this area, it is impossible to make a recommendation; however, it appears that these patients could respond less well if switched to a biosimilar. In any case, it is the clinical response that finally counts," commented Prof Braun.

Several studies[2-4] have recently suggested that a positive MRI suggestive of axSpA according to the Ankylosing Spondylitis Disease Activity Score (ASDAS) definition[6] is frequently found in individuals who do not have axSpA. Thus, there is considerable background noise that is not indicative of axSpA, with MRI scans appearing positive in 6.4% of patients with chronic back pain, 57.1% of post-partum females, and 12.5% of runners, as well as 23.4% of healthy volunteers.[4] Prof Braun further explained that "although lesions are most frequently indicative of axSpA, one should look at the complete clinical picture and not make a diagnosis based on classification criteria alone. What may help to distinguish axSpA from non-axSpA patients are the deep lesions characterised by a large bone marrow oedema present in several slices." In addition, Prof Braun encouraged the use of the ASDAS:[6] "It provides very clear cut-off points that can really help you differentiate between inactive, moderate, high, and very high disease activity, as well as treat-to-target recommendations to help you combat inflammation and prevent structural changes."

Similarly to patients with axSpA, patients with RA who are responding well to the reference biologic treatment may benefit from a switch to a biosimilar. According to Prof Braun, clinical parameters used to assess disease activity should include prognostic factors that are predictors of poor outcomes (Figure 1).[7] On that basis, therapy should be started as early as necessary to induce remission. In terms of imaging techniques, Dr Sengupta primarily discussed the use of X-ray and ultrasound (Figure 1): "If X-rays of hands and feet show clear progression of erosions, [the HCP] should investigate if the patient is taking the medication correctly or where the issue lies before considering switching the patient." Similarly, ultrasound has been shown not to have an additional diagnostic value in routine practice[8] but, according to Dr Sengupta, may have an educational role in symptomatic patients without clinical signs of active disease by reassuring them that their disease is controlled.

Re-evaluating Healthcare Provider–Patient Communication

Evaluating clinical and imaging parameters can help assess disease state prior to considering a switch. Patients expected to maintain a good treatment response when switched to a biosimilar should then be introduced to the switch through shared, informed decision-making. For this, HCP should tailor their patient communication to meet individual patient needs and build their confidence in the treatment. This will not only affect the patient's perception of the biosimilar but will provide the patient with the tools to maximise treatment outcomes. As Dr Sengupta highlighted: "It is crucial that the patients accept what is about to happen, as this increases the possibility of a successful switch. We might debate the pathway and how we get the patient's acceptance, either via a letter and/or face-to-face discussion, but the principle is that the patient has to understand that the biosimilar will be as effective as the reference biologic." Prof Enck therefore encouraged HCP to consider the importance of the patient relationship: "The prescribing physician can have a significant impact on the perceived pharmacological effect of a drug. Communication is much more important than anything you will prescribe to the patient, as it is your communication that drives what the patient will report, regardless of the drug."

Prof Taylor noted that "each physician works in a very different context in which shared, informed decision-making, although ideal, may or may not be an option. However, in each situation there may be patient anxieties that we as physicians have a responsibility to address in a positive, constructive, and compassionate manner." So, how should a HCP tackle patient communication when switching? According to Prof Enck, "no size fits all but there are certain dos and don'ts

that should be considered (Figure 2); we should aim to use these appropriately in different settings to ensure that the correct message is conveyed to the patient in the right way, taking an average of 5–10 minutes, and therefore adhering to the time constraints of a busy clinic. In essence, we are talking about shared decision-making. If you [the HCP] make the decision to switch a patient but are not convinced yourself, then you cannot convince the patient that biosimilars are the best treatment choice. Only if you discuss the options with the patient and tell them what is best for whom, for society, for you as a HCP, and for the patient, then it becomes shared decision-making. Biosimilars are one of the options patients should take; they are the medicine of the future." Accordingly, Prof Braun highlighted that "if the patients had to pay themselves, then the discussion would be very short. I always make three points: the biosimilar is a good drug, it has been tested heavily, it is almost the same, it does not have any clinically meaningful differences compared to the reference biologic; the biosimilar is a very effective drug; and it is good for society as it allows you [the HCP] to treat as many patients as possible; you [the patient] have an opportunity to contribute to that."

Furthermore, the nocebo effect is a topic of interest when discussing best practices; the nocebo effect is the negative equivalent of the placebo effect and has been shown to negatively influence treatment adherence and outcomes in multiple pathologies.[9]

Dos and don'ts

✓ **Speak to the patient** before the switch	✗ Don't leave the patient alone with only **written information**
✓ Talk about **health-economic benefits** of a non-medical switch	✗ Don't proactively discuss potential **AE** that may or may not occur; address them only if the patient asks
✓ Find out where patients collect **information***	✗ Don't blame **Dr Internet**; it is the only source of information available to patients
✓ Talk about **their concerns**	✗ Never use the term **'nocebo'**; it will make the patient feel that you are not taking them seriously
✓ Talk about **your concerns**†	✗ Don't use the words **'cheaper'**; biosimilars are less expensive
✓ Proactively arrange for **feedback** after the switch	✗ Don't talk about **statistics**; patients do not understand them
✓ Offer them a **compromise** 6 months before an alternative therapy is considered	✗ Don't take a patient's **agreement** for granted
✓ Encourage contact with **successful switchers**	✗ Don't push patients for an **immediate decision**

Figure 2: Dos and don'ts of healthcare professional–patient communication.

*More side effects are reported by patients who use the internet. †Costs or pressure from health insurance or representatives.

AE: adverse effects.

Prof Enck highlighted that "the nocebo effect is not unique to reference biologic-to-biosimilar switch but occurs in all medical specialities, whether switching from a branded to a generic drug or from one drug to the next. Patients are always reluctant and sceptical about change." HCP should therefore not automatically dismiss patient-reported adverse events (AE) as being a nocebo effect; it is important to acknowledge the symptoms appropriately.

The use of an information leaflet or letter to replace or support the prescribing physician's face-to-face consultation when switching a patient was comprehensively debated among the faculty. Patients may not retain the information provided during the consultation and instead seek information independently. Providing an information leaflet or letter has successfully supported switches in Prof Taylor's and Dr Sengupta's practices in the UK: "Written information should be simple, short, and clear, giving the patient a rationale for the switch, both from the clinical and the health-economic perspective, as well as provide contact details for the patients to use in case of queries or concerns," clarified Dr Sengupta. In comparison, Prof Braun felt that the use of a letter in his practice in Germany would be insufficient from a legal perspective and should be supplemented with verbal communication in the practice in order to be effective and safe. To address this need, the German Ministry of Health is investing in the education of nurses specialising in rheumatology and in structured patient education programmes. According to Dr Sengupta, communication via social media channels could also be an additional resource: "The younger patients definitely use social media, helplines, and fora. Collaborating with national charities can ensure that correct information is available online, helping patients understand the concept of biosimilars."

Patients may react differently to the idea of switching. However, according to Dr Sengupta, the most frequent patient query is why they should switch when they are doing well on the reference product. Both Dr Sengupta and Prof Braun suggested that an honest approach should be used: "Explain the available studies and show the patient that the biosimilar has been tested extensively and it is as clinically effective as their current treatment.

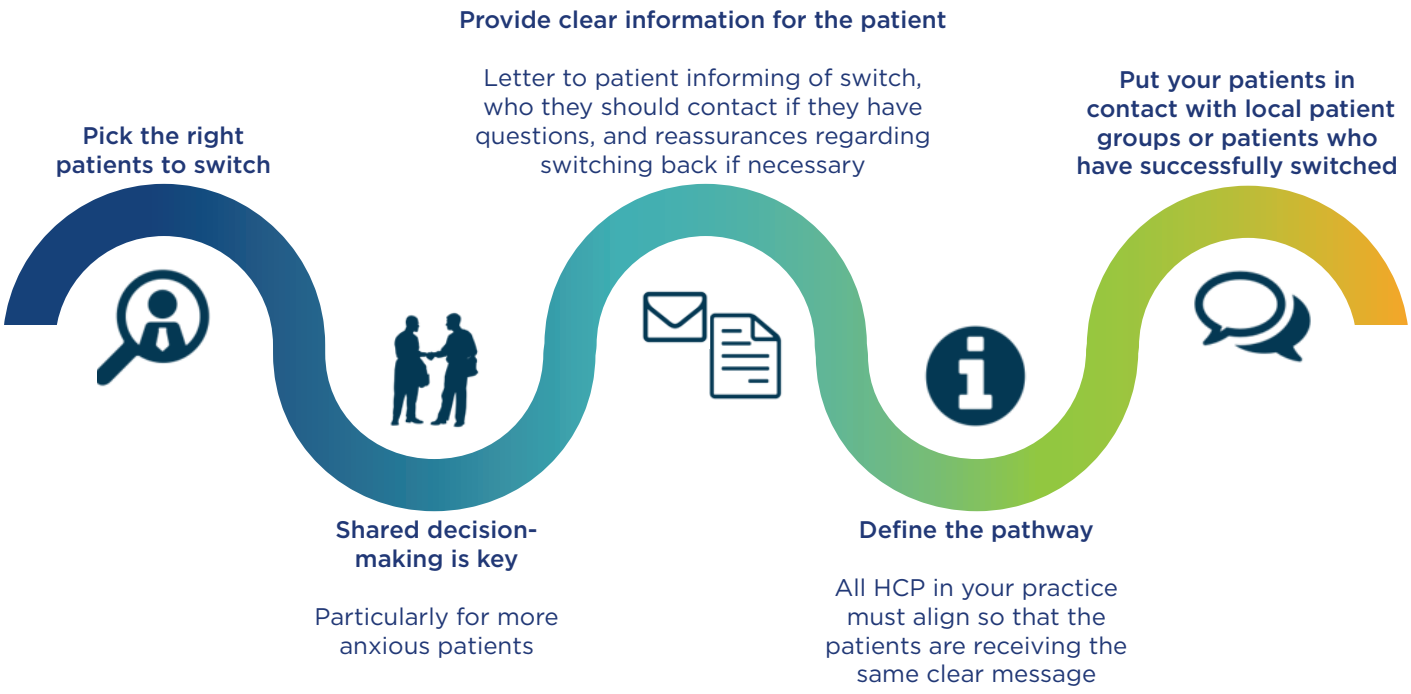


Figure 3: A pathway to successful switching.

HCP: healthcare professional.

Reassure them that you believe they will maintain a good response. Discuss the societal benefits of switching, how these drugs are less expensive and will allow more patients to be treated with effective therapies," explained Dr Sengupta. In agreement, Prof Enck added: "When switching to a biosimilar, it is not necessary to start the discussion about AE unless the patient initiates the conversation; from what we know, the biosimilars are very similar to the reference product and singling them out by talking about AE will just increase the patient's anxiety, causing the patient to expect the AE." Similarly, Dr Sengupta suggested avoiding priming the patient by telling them that they will be given an opportunity to switch back to the reference product: "This is not something I would standardly bring up. If the patient asks, I do provide assurance that we can."

Successful Switching

Successful switching practices will vary across different countries, healthcare systems, and individual practices. Both Dr Sengupta and Prof Braun agreed that following a simple set of guidelines (Figure 3) was effective in their clinical centres, resulting in 90% of their patients with RA and axSpA remaining on biosimilar treatment post-switch. Dr Sengupta also confirmed that disease activity scores remained comparable between pre and post-switch patients. Also, in Norway, where the tender system is in effect, Prof Haugeberg reported that only 10% of patients requested to switch back to the reference biologic, suggesting that the use of a non-medical switch, whereby HCP are encouraged to prescribe a biosimilar as a matter of course, has not significantly affected treatment adherence rates.[10]

Post-Switch Monitoring

Prescription of any biologic therapy requires careful follow-up to ensure that the treatment is safe and effective. Follow-up visits can enable patients to address any concerns or queries they may have. However, as Prof Haugeberg explained, as disease control improves, frequent monitoring of patients in-clinic may become redundant: "In Norway, between 2004 and 2013, the proportion of RA patients in remission increased from 20% to 55%. This caused us to rethink how we monitor patients: do they all need to take time out in their busy schedule to attend a clinic appointment, only to be told they are fine?"

This question motivated Prof Haugeberg to participate in the initiation of an app, a remote monitoring tool currently being tested in Norway. Prof Haugeberg explained: "Patients need a simple tool with brief questions that they can answer at their own leisure in a place of their choice, which they can use to report how they feel. This can be done through a smartphone app that prompts the patient to regularly give simple feedback of well-known patient reported outcome data to the physician or nurse. This system can also support patients in deciding when they should be requesting follow-up appointments or when the monitoring can continue online. This has the potential to free up a significant amount of time for the clinic and shortens the waiting lists for an appointment. It also allows us to monitor the patients remotely." To be compliant with data privacy rules, a remote monitoring tool needs to be securely encrypted and anonymised appropriately. Patients need to retain control of their personal data and the ability to request its deletion. "In Norway, we have a whole separate department within the health authorities to ensure compliance with all data protection laws," commented Prof Haugeberg.

Conclusion

Confidence in biosimilars has grown alongside the volume of robust clinical trials and real-world evidence that has become available. Combined with the potential for significant cost savings, biosimilars offer healthcare systems the opportunity for sustainable treatment of rheumatic conditions. Furthermore, the endorsement of reference biologic-to-biosimilar switching by regulatory bodies in Europe has shifted the discussion towards questions around best practices for

the effective implementation of biosimilars in the clinic. Here, key experts discussed clinical, imaging, psychosocial, and monitoring practices that can be used to ensure an optimal treatment response when switching a patient to a biosimilar.

When switching is not compulsory, careful selection of stable patients suitable for switching, by accurately measuring prognostic factors using both clinical and imaging tools, was advised. HCP–patient communication was deemed vital to an effective switch, with the HCP's confidence in the biosimilar and the use of shared decision-making considered essential aspects in the process. Finally, regarding evolving technologies, online platforms and apps have provided significant opportunities for remote monitoring, bringing a new element to clinical management and assessment of disease remission. Simple remote monitoring tools could free significant resources for the practice, while allowing the HCP to follow a patient without either being constrained by clinical appointments. Prof Taylor concluded: "The faculty has provided very thoughtful comments that need to be applied in the cultural context in which each of us works. It is not necessarily the case that one approach to communication will suit everybody, but it is the case that we have the potential for very significant health-economic savings in the environment that we live in."

References

1. Rovira J et al. Biosimilars in the European market. GaBI Journal. 2013;2(1):30-5.
2. de Bruin F et al. Prevalence of degenerative changes of the spine on magnetic resonance images and radiographs in patients aged 16–45 years with chronic back pain of short duration in the spondyloarthritis caught early (SPACE) cohort. Rheumatology. 2016;55(1):56-65.
3. Chang HJ et al. Osteoarthritis of the lumbar spine. JAMA. 2010;304(1):114.
4. de Winter J et al. An ASAS-Positive MRI of the sacroiliac joints can also occur in healthy individuals, runners and women with postpartum back pain. Arthritis Rheumatol. 2018;70(7):1042-8.
5. Song IH et al. Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): A 48-week randomised controlled trial. Ann Rheum Dis. 2011;70(4):590-6.
6. Ramiro S et al. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. Ann Rheum Dis. 2014;73(8):1455-61.
7. Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76(6):960-77.
8. Haavardsholm EA et al. Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. BMJ. 2016;354:4205.
9. Rezk MF, Pieper B. Treatment outcomes with biosimilars: Be aware of the nocebo effect. Rheumatol Ther. 2017;4(2):209-18.
10. Glintborg B et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. Ann Rheum Dis. 2017;76(8):1426-31.

Abstract Reviews

A selection of riveting reviews of abstract presentations from the EULAR 2018 Congress

Treating Rheumatoid Arthritis to Target: Is Low Disease Activity Good Enough?

Authors: *Elena Nikiphorou,[1] Sam Norton,[1] Adam Young,[2] Lewis Carpenter,[1] Josh Dixey,[3] David Walsh,[4] Patrick Kiely[5]

1. Academic Rheumatology Department, King's College London, London, UK
2. Life Sciences Department, University of Hertfordshire, Hertfordshire, UK
3. Rheumatology Department, The Royal Wolverhampton, Wolverhampton, UK
4. Rheumatology Department, The University of Nottingham, Nottingham, UK
5. Rheumatology Department, St George's Hospital, London, UK

*Correspondence to enikiphorou@gmail.com

Disclosure: The authors have declared no conflicts of interest.

Keywords: Disease activity score (DAS) 28-joint count (DAS28), remission, rheumatoid arthritis (RA), treat-to-target.

Citation: EMJ Rheumatol. 2018;5[1]:44-45. Abstract Review No. AR1.

Treat-to-target principles in rheumatoid arthritis (RA) are now widely recognised as effective in achieving optimal disease outcomes. This study examined differences in outcomes between low (LDAS) and remission (RDAS) disease activity score (DAS) categories, addressing whether LDAS is an acceptable treatment target in RA.

Data from two consecutive UK multicentre RA inception cohorts with similar designs were used: the Early RA Study and the Early RA Network. Recruitment figures and median follow-up for the Early RA Study and Early RA Network were 1,465 and 10 years (maximum 25 years), and 1,236 and 6 years (maximum 10 years), respectively. Standard demographic and clinical variables were recorded at baseline and then annually until the end of study follow-up. Disease activity was categorised as remission (mRDAS <2.6) or low (mLDAS 2.6–3.2) using mean DAS 28-joint count (DAS28) score between Years 1 and 5; classification also included sustained low/remission DAS (sLDAS/sRDAS), based on DAS persisting in each of the two categories at Years 1–2, and Boolean remission (Years 1–2). Change in Health Assessment Questionnaire (HAQ) and 36-item Short Form Survey (SF36) (physical [PCS] and mental [MCS] components) for each disease activity category were modelled using linear mixed models

with time incorporated as a linear spline with change-point at 12 months. Year of onset, age, sex, and use of steroids or conventional disease-modifying antirheumatic drugs at first visit were included as covariates. From a total of 2,701 patients across the two cohorts, 468 (17%) were in mRDAS and 284 (11%) in mLDAS in the first 5 years of disease. Lower proportions of patients achieved sRDAS (8%), sLDAS (6%), and Boolean remission (2%). Mean age was similar across categories but more women were in LDAS versus RDAS. Compared to mLDAS or sLDAS, inflammatory markers, DAS, functional (HAQ, PCS) scores, and mental (MCS) scores tended to be better in the mRDAS, sRDAS, and Boolean remission categories. Significant differences ($p<0.05$) were noted between the mRDAS and mLDAS between Years 1 and 5 for all outcomes; for sRDAS compared to sLDAS, the difference was significant at Year 1 but not by Year 5. Figure 1 shows disability (HAQ) and SF36 (PCS and MCS) for each disease activity category.

In summary, this study demonstrates striking differences between RDAS and LDAS categories, suggesting worse functional and SF36 outcomes over time in the LDAS categories. This is an important observation because it justifies striving for remission in RA to improve patient outcomes. The study therefore concludes that remission should be the primary treat-to-target goal in RA.

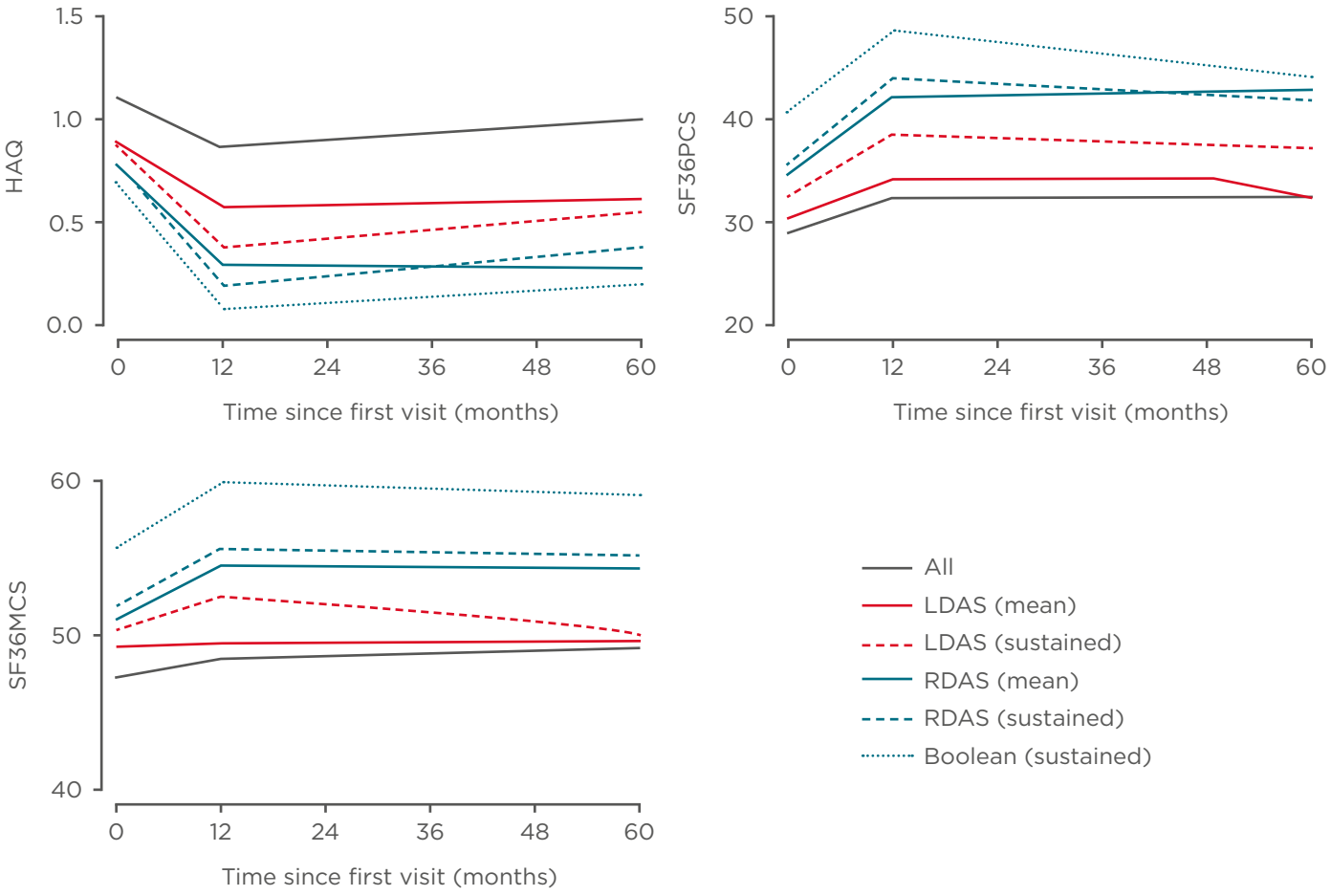


Figure 1: Health Assessment Questionnaire and 36-item Short Form Survey outcomes by disease activity category.

HAQ: Health Assessment Questionnaire; LDAS: low disease activity score; RDAS: remission disease activity score; SF36MCS: 36-item Short Form Survey mental component score; SF36PCS: 36-item Short Form Survey physical component score.

Physician Global Assessments for Disease Activity in Rheumatoid Arthritis Are All Over the Map!

Authors: Matthew A. Turk,[1] *Janet E. Pope[1,2]

1. Western University, Schulich School of Medicine and Dentistry, London, Canada
2. St. Joseph's Health Care, London, Canada

*Correspondence to janet.pope@sjch.london.on.ca

Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: The authors would like to thank members of the Canadian Rheumatology Association (CRA) who responded to this survey.

Keywords: Outcome measurement, physician global assessment, rheumatoid arthritis (RA).

Citation: EMJ Rheumatol. 2018;5[1]:46-47. Abstract Review No. AR2.

There have been many studies about patient global assessments of disease activity in rheumatoid arthritis (RA) and how these differ from physician global assessments (MD global).[1] The studies measure different things; when the rheumatologist is assessing patients with RA, disease activity is often based on swollen joints, their severity and distribution, and inflammatory markers, whereas patients may base their assessment on pain, damage, other musculoskeletal problems, and how they have been feeling recently, as opposed to disease activity. Physicians only see patients at a certain point in time, whereas patients may have flares and improvements of disease activity between visits; the latter would not be captured in the MD global if the flare had resolved.

The current study, presented at the European League Against Rheumatism (EULAR) 2018 Congress in Amsterdam, Netherlands, sent questionnaires to rheumatologists who are members of the Canadian Rheumatology Association (CRA) about patient scenarios of varying RA disease activity. They were asked to rate the disease activity on a scale of 0–10 for each case.[2] Some cases involved follow-up visits so that the change in global assessment could be calculated. There was a response rate of approximately 30%.

The results showed that there was a wide variability of global assessments, but there was more agreement for extreme cases (low disease activity and high activity) (Figure 1). The cases in between these extremes had wide variability between physicians and little agreement. Agreement was in consensus for the change in global assessments for the scenarios that had follow-up visits, suggesting that rheumatologists may not agree on the score of disease activity but the change in activity was congruent (such as a lot worse, worse, same, better, or a lot better) as measured by a change in the global assessments. Rheumatologists who ranked themselves as experts in RA gave higher disease activity scores, which could mean that they did not tolerate disease activity and ranked any activity higher. The authors predicted that the scores of RA experts would be lower than their less experienced colleagues as they have seen so many cases and would be able to better contextualise a 10/10 score.

This study is limited by focussing on cases on paper, rather than assessing real patients.

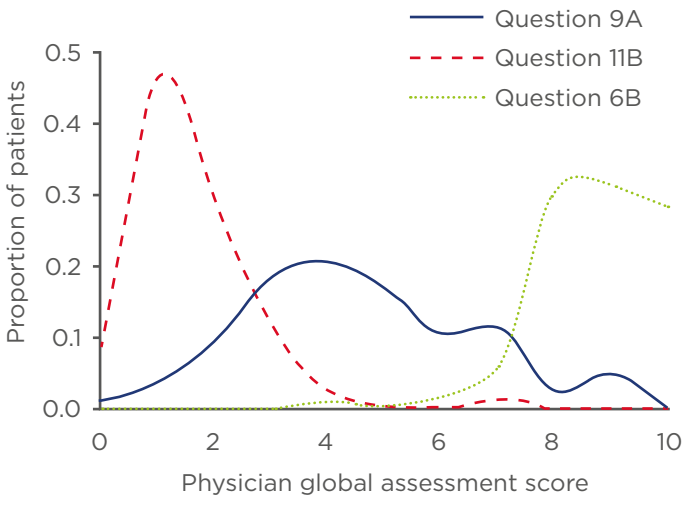


Figure 1: Global assessments of rheumatoid arthritis cases.

Cases that are extreme have more agreement than medium cases, as illustrated by the distribution of responses from these three scenarios.

The authors also had discordant patient global assessments wherein, for instance, a patient could be seen with no disease activity but ranked their pain and activity as 4/10, because this reflects real-world patients. In clinical practice, treating to a target includes low disease activity or remission as a goal so MD global should ideally be more standardised. This reflects what happens in the real world, and so there could be training for rheumatologists with a catalogue of scenarios to reach a better consensus (such as with a Delphi exercise) and it may mean that training for RA clinical trials is important since some scores have MD global in them (clinical [CDAI] and simple disease activity indices [SDAI])[3] and remission rates can be very different depending on global assessments.

References

1. Rohekar G, Pope J. Test-retest reliability of patient global assessment and physician global assessment in rheumatoid arthritis. J Rheumatol. 2009;36(10):2231-7.
2. Turk MA, Pope J. Physician global assessments for disease activity in rheumatoid arthritis are all over the map! Ann Rheum Dis. 2018;77(Suppl 2):854-55.
3. Aletaha D, Smolen J. The simplified disease activity index (SDAI) and the clinical disease activity index (CDAI): A review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol. 2005;23(5 Suppl 39):S100-8.

Linking Systemic Angiogenic Markers to Synovial Vascularisation in Rheumatoid Arthritis

Authors: Agathe Leblond,[1] Sonia Pezet,[1] Anne Priscille Trouvin,[2] Muriel Elhai,[2] Virgine Gonzalez,[1] Yannick Allanore,[2] *Jérôme Avouac[2]

1. Université Paris Descartes, Sorbonne Paris Cité, INSERM U1016 and CNRS UMR8104, Institut Cochin, Paris, France
2. Service de Rhumatologie A, Hôpital Cochin, Université Paris Descartes, Sorbonne Paris Cité, Paris, France

*Correspondence to jerome.avouac@aphp.fr

Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: Grant support for this work was provided by Appel d'Offre Interne de l'Hôpital Cochin – MERRI Performances des Etablissements de Santé dans la Promotion de la Recherche and Arthritis Foundation.

Keywords: Angiogenic markers, power Doppler ultrasound (PDUS), rheumatoid arthritis (RA), synovial vascularisation.

Citation: EMJ Rheumatol. 2018;5[1]:47-49. Abstract Review No. AR3.

The synovium is the primary site of the rheumatoid arthritis (RA)-related inflammatory process. One of the most noticeable signs of synovitis is the amount of synovial vascularisation, which is critical for synovial proliferation and invasiveness.[1] Previous studies have showed the considerable ability of highly sensitive power Doppler ultrasound (PDUS) to improve the scoring of synovitis by detecting extended synovial vasculature.[2] Only scarce data are currently available regarding correlations between systemic angiogenic activity, measured by angiogenic factors in the serum, and the amount of local synovial vascularisation, measured by Doppler ultrasound.[3] The objective of this study was to investigate associations between synovial vascularity assessed by PDUS and a panel of eight serum vascular markers reflecting different angiogenic processes, such as endothelial cell activation, proliferation, survival, growth, and migration, as well as vessel maturation and stabilisation.

Serum levels of eight angiogenic markers (vascular endothelial growth factor, placenta growth factor [PlGF], Tie-2, angiopoietin-1, soluble vascular cell adhesion molecule-1 [sVCAM-1], IL-8 [CXCL8], CYR61 [CCN1], and angiostatin) were measured by quantitative ELISA in a total of 125 RA patients. The study participants were all systematically assessed in parallel by PDUS, performed on 32 joints.

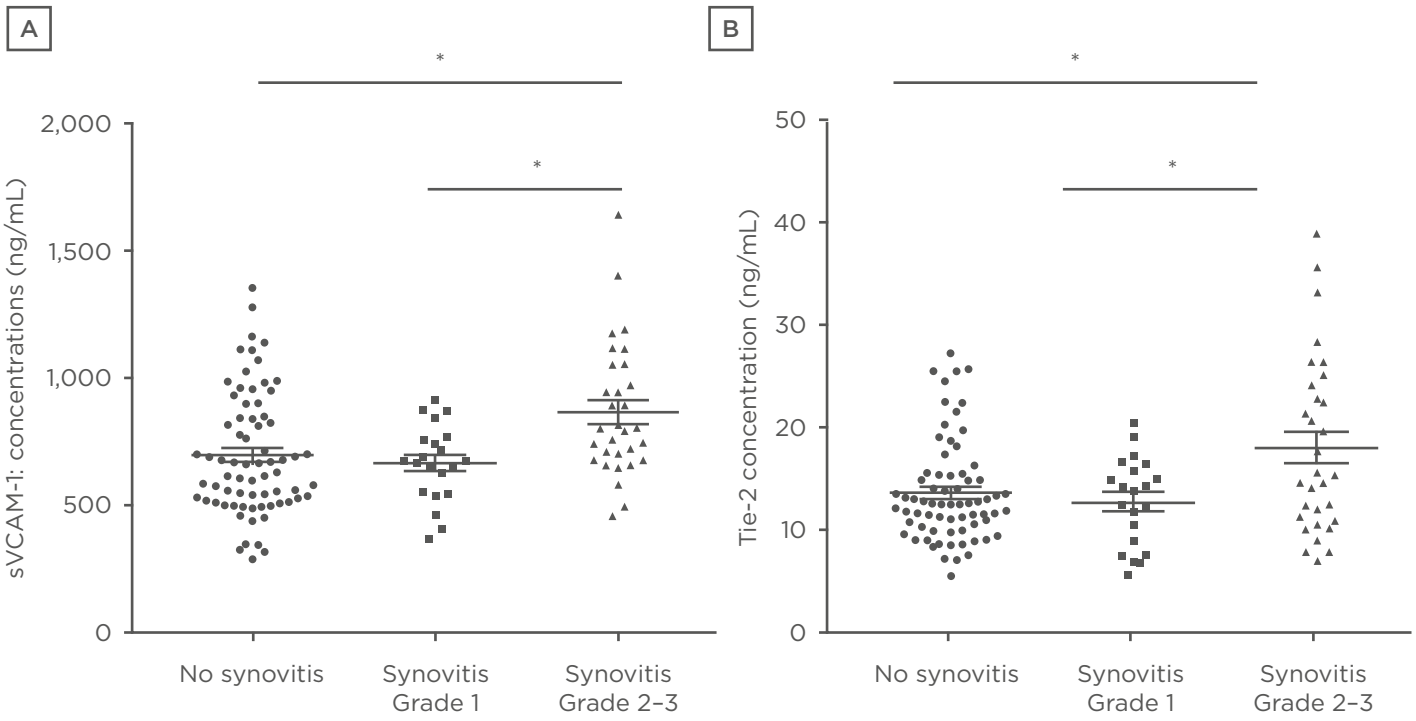


Figure 1: Levels of soluble vascular cell adhesion molecule-1 (A) and Tie-2 (B) according to the intensity and extent of synovial vascularisation assessed by power Doppler ultrasound.

Statistical analysis involved an analysis of variance (ANOVA) test followed by Tukey's multiple comparisons test.

*p<0.01

sVCAM-1: soluble vascular cell adhesion molecule-1.

A global synovitis score, derived from the Global OMERACT-EULAR Synovitis Score (GOESS), was calculated for the 16 paired joints using the sum of the composite PDUS scores for all joints examined, giving a potential score of 0–96.

Synovitis was detected in 84 patients with RA (67.2%). Among these patients, 53 patients (42.4%) had a positive Doppler signal, including 31 with moderate-to-marked hyperaemia. Serum levels of sVCAM-1 (808±293 ng/mL versus 697±240 ng/mL; p=0.022) and Tie-2 (16.2±7.5 ng/mL versus 13.8±4.9 ng/mL; p=0.038) were more likely to be increased in patients with synovial hyperaemia detected on at least one joint (power Doppler Grade ≥1). sVCAM-1, Tie-2, and angiostatin concentrations gradually increased together with the grade of the semiquantitative PDUS scale, and concentrations of these three markers were markedly increased in patients with moderate-to-marked hyperaemia (power Doppler Grades 2 and 3) (Figure 1). Levels of sVCAM-1 (r=0.20; p=0.028), Tie-2 (r=0.28; p=0.001), and angiostatin (r=0.25; p=0.006) correlated with a global arthritis sum score, defined by the sum of the semiquantitative PDUS scores for all joints examined.

Among the 81 patients with a Disease Activity Score 28-joint count C-reactive protein ≤3.2, 22 patients had synovial hyperaemia detected on at least one joint (power Doppler Grade 1 in 13 patients, Grade 2 in 6 patients, and Grade 3 in 3 patients). Patients with synovial hyperaemia on at least one joint were more likely to have significantly increased levels of PlGF (18.9±11.2 pg/mL versus 13.1±9.5 pg/mL; p=0.022) and Tie-2 (15.7±5.8 ng/mL versus 12.6±3.4 ng/mL; p=0.004) than patients without synovial hyperaemia.

In conclusion, serum levels of the angiogenic markers Tie-2, sVCAM-1, and angiostatin were strongly associated with synovial vascularisation and inflammation assessed by PDUS among patients with established RA. Moreover, Tie-2 and PlGF were associated with persistent disease activity. These data highlight the possibility of

identifying surrogate serum angiogenic markers of active synovitis and the need to confirm their pertinence in longitudinal studies.

References

1. Leblond A et al. Targeting synovial neoangiogenesis in rheumatoid arthritis. Autoimmun Rev. 2017;16(6):594-601.
2. D'Agostino MA et al. Scoring ultrasound synovitis in rheumatoid arthritis: A EULAR-OMERACT ultrasound taskforce-Part 1: Definition and development of a standardised, consensus-based scoring system. RMD Open. 2017;3(1):e000428.
3. Nordal HH et al. Calprotectin (S100A8/A9) has the strongest association with ultrasound-detected synovitis and predicts response to biologic treatment: Results from a longitudinal study of patients with established rheumatoid arthritis. Arthritis Res Ther. 2017;19(1):3.

Development and Implementation of an Educational Video That Instructs Patients with Rheumatoid Arthritis for Self-Assessment of Disease Activity: Methodology of the AUTO-DAS in Middle Eastern Arab Countries Study

Authors: *Nelly Ziade,[1] Ghada Abi Karam,[1] Amani Daher,[1] Mohammad Abu Jbara,[2] Alla Ayko,[3] Elie Alam,[4] Thurayya Arayssi,[5] Humeira Badsha,[6] Samar el Emadi,[7] Hussein Halabi,[8] Ghita Harifi,[6] Bhavna Khan,[9] Lina el Kibbi,[10] Manal al Mashaleh,[11] Abdel Fattah Masri,[12] Bassel Masri,[13] Jeanine Menassa,[14] Mira Merashli,[12] Georges Merheb,[15] Jamil Messaykeh,[16] Kamel Mroue',[17] Sahar Saad,[18] Nelly Salloum,[19] Imad Uthman,[12] Bassel el-Zorkany[20]

1. Saint-Joseph University, Beirut, Lebanon
2. Al-Bashir Hospital, Amman, Jordan
3. Al Rassoul al-Aazam Hospital, Beirut, Lebanon
4. Levant Hospital, Beirut, Lebanon
5. Weill Cornell Medicine, Doha, Qatar
6. Dr Humeira Badsha Medical Center, Dubai, United Arab Emirates
7. Hamad Medical Corporation, Doha, Qatar
8. King Faisal Specialist Hospital, Jeddah, Saudi Arabia
9. Mediclinic City Hospital, Dubai, United Arab Emirates
10. Al Faisal University, Riyadh, Saudi Arabia
11. King Hussein Medical Center, Amman, Jordan
12. American University of Beirut, Beirut, Lebanon
13. Jordan Hospital, Amman, Jordan
14. Lebanese University, Beirut, Lebanon
15. Holy-Spirit University, Kaslik, Lebanon
16. Monla Hospital, Tripoli, Lebanon
17. Al-Zahraa Hospital, Beirut, Lebanon
18. King Hamad University Hospital, Al Sayh, Bahrain
19. Registered nurse, Beirut, Lebanon
20. Cairo University, Cairo, Egypt

*Correspondence to nellziade@yahoo.fr

Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: The authors would like to acknowledge Prof Maxime Dougados, Cochin Hospital, France, and the National Rheumatoid Arthritis Society, Maidenhead, UK for providing access to the video used with patients in France and the UK, respectively, and granting us authorisation to use these videos as a reference to create our own educational video.

Keywords: Disease Activity Score (DAS), patient education, patient-reported outcomes, rheumatoid arthritis (RA), self-assessment.

Citation: EMJ Rheumatol. 2018;5[1]:49-51. Abstract Review No. AR4.

BACKGROUND

The treat-to-target concept has revolutionised rheumatoid arthritis (RA) management and prognosis.[1] Using a specific treatment target, such as Disease Activity Score (DAS)-28, and involving patients in their disease management can help to improve disease prognosis.

The objective of this study was to develop and implement an educational video that instructs patients with RA how to carry out a self-assessment of disease activity using DAS-28.

METHODS

Step 1: Identify the Unmet Needs in Rheumatoid Arthritis Evaluation and Plan the Study

Rheumatologists from some Middle Eastern Arab countries (MEAC) were invited to participate in this study. The protocol draft was presented during regional meetings to identify the unmet needs in RA patients and to finalise the study protocol. International experts and societies were contacted to access pre-existing educational material.

Step 2: Adapt the Protocol and Produce the Educational Material

Different material sources[2-5] were synthesised and translated into Arabic through a professional translation service, and specific medical terms were translated by the rheumatologists themselves. The Arabic text and English subtitles were validated by the rheumatologists through multiple email rounds. The simplified leaflet was developed in both Arabic and English languages. The educational video was shot by a professional team with a real patient and a rheumatologist on set. The voiceover was recorded with the presence of one of the medical team members in the studio.

Step 3: Validate the Educational Material

The final products (leaflet, text, subtitles, and video) were validated by the rheumatologists through email rounds. The material was tested on RA patients to assess comprehension and acceptability. Obstacles were noted at the various study levels.

RESULTS

A total of 23 rheumatologists from 7 MEAC participated in the study. A one-page educational leaflet was developed in both Arabic and English languages. An educational video presenting the treat-to-target concept and the basics of DAS performance in a simple way was produced with a voiceover in the Arabic language with English subtitles.[6] Obstacles experienced at the rheumatologist, patient, cultural, and logistical levels were identified (Table 1) and the potential solutions were addressed by the study team. The solutions will be applied in the future steps of the Auto-DAS MEAC study.

Table 1: Obstacles faced during the conception and implementation of the educational tool for rheumatoid arthritis patient empowerment for self-assessment at the different levels: rheumatologist, patient, cultural, and logistical.

Obstacles to the development and implementation of the educational material			
Rheumatologist level	**Patient level**	**Cultural level**	**Logistical level**
Approve DAS as a proper treatment target.	Accept the idea of patient empowerment.	Produce a uniformly acceptable and comprehensible written Arabic text despite different dialects.	Obtain IRB approvals from different institutions in a timely manner.
Accept the idea of patient empowerment.	Understand some of the video parts on how to properly examine certain joints.	Produce an educational video that is culturally acceptable across different countries.	Obtain nonbiased funding source.
Be skeptical about patient adherence to the use of the provided tool.	Have low confidence level about the correct performance of the self-assessment.	Address the population cultural mix in some countries.	Use computerised data source instead of papers.

DAS: Disease Activity Score; IRB: Institutional Review Board.

CONCLUSIONS

Collaboration between several countries sharing the same language and similar cultural backgrounds and unmet needs was possible and allowed for the production of an educational material aimed at the empowerment of RA patients for the self-assessment of their disease activity. Obstacles to applying self-assessment were identified, and potential solutions will be applied to the future steps of the Auto-DAS MEAC study. The video will serve for future studies in Arabic-speaking countries and will be available for clinical use according to the rheumatologist's clinical judgment.

Discussions with experts during the abstract display at the European League Against Rheumatism (EULAR) Congress in Amsterdam, Netherlands, yielded additional comments about the obstacles identified in Table 1, mainly surrounding the use of DAS as a proper treatment target. Several suggestions were made about the proper tool to adopt, which will be highly useful for the future steps of the study.

References

1. Smolen JS et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis. 2016;75(1):3-15.
2. Gossec L et al. Is the self-assessment of disease activity (auto-DAS28) by patients a feasible and acceptable measure over the long term in rheumatoid arthritis? Three-year follow-up of a nurse-led program in 771 patients with establish RA [Abstract]. Arthritis Rheumatol. 2016;75(Suppl 2).
3. Sordet C et al. Comparison of self assessment of disease activity to Das28 in rheumatoid arthritis: Data from the randomized "Roc" trial. [Abstract]. Ann Rheum Dis. 2016;75(Suppl 2):408.
4. National Rheumatoid Arthritis Society. Know your DAS: App (Mobile and Tablet). Rheumatoid Arthritis Management Tool. 2016. Available at: https://www.nras.org.uk/know-your-das-mobile-app. Last accessed: 18 June 2018.
5. DAS28. 2018. Available at: https://www.das-score.nl/das28/en/. Last accessed: 18 June 2018.
6. Khasha G. YouTube. AUTO-DAS Middle Eastern Arab Countries. 2018. Available at: https://www.youtube.com/watch?v=32EQgPMGqDA. Last accessed: 18 June 2018.

Adiponectin Level, Insulin Resistance, and Endothelial Dysfunction in Hypertensive Females with Rheumatoid Arthritis

Authors: *Oksana Sirenko

Olexander Kuryata Institution, Dnipropetrovsk Medical Academy, Dnipro, Ukraine
*Correspondence to oksanasirenko@i.ua

Disclosure: The author has declared no conflicts of interest.

Keywords: Atherosclerosis, cardiovascular risk factors, hypertension (HT), rheumatoid arthritis (RA).

Citation: EMJ Rheumatol. 2018;5[1]:51-52. Abstract Review No. AR5.

Rheumatoid arthritis (RA) is associated with accelerated atherosclerosis and high cardiovascular mortality. Cardiovascular risk assessment in RA patients with comorbid hypertension (HT) does not fully reflect traditional risk scales, thus inclusion of additional factors when diagnosing these patients is required.

OBJECTIVES

The aim of the study was to estimate the adiponectin level, insulin resistance, and endothelial function in RA females with comorbid HT and investigate the relationship with subclinical manifestations of atherosclerosis.

MATERIALS AND METHODS

The study included 82 RA females with low disease activity and comorbid HT (mean age: 54.6 years, range: [49.7–62.5]) and 40 HT females without RA (control group). All patients received stable RA therapy for >6 months. Patients with

coronary artery disease were excluded. The risk of fatal cardiovascular disease was calculated using mSCORE and RA disease activity was measured using the Disease Activity Score including a 28-joint count (DAS28) scale. Carotid ultrasound detection and endothelial-dependent flow-mediated vasodilatation were performed using the Celermajer method. The levels of adiponectin and insulin were measured using ELISA and insulin resistance was estimated using the homeostatic model assessment (HOMA2) index.

RESULTS

Endothelial dysfunction was established in most study group patients: 61 patients (74.4%); insulin resistance was shown in 70 patients (85.4%) and elevated levels of adiponectin in 35 patients (42.7%). Hypertensive females with RA had significantly higher adiponectin, insulin, and insulin resistance levels compared to the control group ($p<0.05$). Subclinical manifestations of atherosclerosis were established in most HT females with RA, while the median cardiovascular risk level was 4.2% [range: 2.7–6.5] matched by mSCORE. The presence of atherosclerotic plaques in HT females with RA was associated with age (odds ratio [OR]: 1.242; p=0.004; 95% confidence interval [CI]: 1.007–1.780), glucocorticosteroid therapy >3 months (OR: 1.56; p=0.001; 95% CI: 1.22–2.45), endothelial dysfunction (OR: 3.584; p=0.001; 95% CI: 1.710–4.723), insulin resistance (OR: 1.684; p=0.011; 95% CI: 1.22–2.74), and abnormal adiponectin level (OR: 1.71; p=0.028; 95% CI: 1.17–2.43). The area under the receiver operating characteristic curve indexes for the prognostic role of adiponectin and HOMA2 in subclinical atherosclerosis development were 0.79 (95% CI: 0.64–0.95; $p<0.05$) and 0.76 (95% CI: 0.61–0.92; $p<0.05$), respectively, indicating good quality diagnostic models.

Thus, an increased frequency of subclinical atherosclerosis manifestation was observed in HT females with RA; however, cardiovascular risk by mSCORE in HT females with RA and subclinical atherosclerosis manifestations showed a dominant, moderate risk. These results support the need for population-specific cardiovascular risk stratification models with the consideration of vascular imaging and potentially the use of novel cardiovascular disease risk biomarkers in HT patients with RA.

CONCLUSION

HT females with RA are characterised by a higher frequency of insulin resistance, endothelial dysfunction, and adiponectin level changes, which are associated with subclinical atherosclerosis manifestations.

Changes in Bone Mineral Density Over 10 Years in Patients with Early Rheumatoid Arthritis

Authors: *Lisa Theander,[1] Minna Willim,[2,3] Jan Åke Nilsson,[1,3] Magnus Karlsson,[4] Kristina Åkesson,[4] Carl Turesson[1,3]

1. Rheumatology, Department of Clinical Sciences, Lund University, Lund, Sweden
2. Rheumatology, Department of Clinical Sciences, Lund University, Lund, Sweden
3. Department of Rheumatology, Skåne University Hospital, Malmö and Lund, Sweden
4. Clinical and Molecular Osteoporosis Research Unit, Department of Clinical Sciences, Lund University, Lund, Sweden

*Correspondence to lisatheander@hotmail.com

Disclosure: The authors have declared no conflicts of interests.

Acknowledgements: The authors would like to acknowledge Dr Christina Book, who initiated this project and performed a major part of the data collection, but sadly passed away before the preparation of this abstract. This study was supported by the Swedish Research Council, the Swedish Rheumatism Association, and Lund University.

Keywords: Bone mineral density (BMD), dual-energy X-ray absorptiometry (DXA), longitudinal survey, osteoporosis, rheumatoid arthritis (RA).

Citation: EMJ Rheumatol. 2018;5[1]:52-54. Abstract Review No. AR6

BACKGROUND

Patients with rheumatoid arthritis (RA) have been shown to have an increased risk of osteoporosis and fractures. Most studies on RA and osteoporosis are cross-sectional and only a few have investigated changes in bone mineral density (BMD) over time.

OBJECTIVE

The objective of this investigation was to study changes in BMD in men and women with early RA over a period of 10 years.

METHODS

An inception cohort of consecutive patients with early RA (N=233, symptom duration <12 months), recruited from 1995–2005, was investigated.[1,2] Patients were followed according to a structured programme, including dual-energy X-ray absorptiometry (DXA) of the left femoral neck and the lumbar spine (L2–L4) at inclusion and after 2, 5, and 10 years. Z-scores (standard deviations above or below the mean BMD for the given age and sex) were calculated using a cohort of healthy individuals from the same area as the reference population. The mean Z-score over the study period was estimated using mixed linear effect models. Changes in Z-scores between follow-up visits were analysed using the paired T-test. Data are presented as mean values with corresponding 95% confidence intervals (CI).

RESULTS

At inclusion, 220 patients were examined with DXA. The corresponding numbers of patients examined at 2, 5, and 10 years were 196, 173, and 122, respectively. Among those with baseline DXA data, the mean age was 60 years, the mean symptom duration was 7.4 months, and 70% of the population were women. Men were older than women (mean age of 63 versus 59 years, respectively) and more often treated with corticosteroids at inclusion (49% versus 35%, respectively). Most of the patients were on disease-modifying antirheumatic drugs (86% of males and 81% of females). More women were treated for osteoporosis (using bisphosphonates and/or calcium and vitamin D), and 16% of the female participants were on oestrogen at inclusion.

At the femoral neck, the mean Z-score over 10 years was -0.07 (95% CI: -0.22–0.08) in women and -0.33 (95% CI: -0.57–[-0.08]) in men. Men had significantly lower BMD at the femoral neck than expected by age at inclusion. The was no significant change in femoral neck Z-scores over time in men and women. At the lumbar spine, the mean Z-score for women was 0.06 (95% CI: -0.10–0.21) and -0.05 (95% CI: -0.29–0.19) for men. There was a significant increase in Z-scores at the lumbar spine over time in both groups.

In the paired comparisons of BMD at different follow-up visits, Z-scores in the femoral neck decreased significantly from inclusion to the 5-year follow-up visit in men (mean change: -0.23 [95% CI: -0.43–(-0.03)]). After 5 years, no further reduction was seen. Lumbar spine BMD Z-scores increased in both men and women over the study period (mean change: 0.36 [95% CI: 0.21–0.52] in women and 0.47 [95% CI: 0.20–0.74] in men).

CONCLUSION

In this study of patients with early RA, men had low femoral neck BMD at the start of the study and kept losing bone mass during the first 5 years of follow-up. Lumbar spine BMD Z-scores in both women and men increased significantly over the study period. Potential explanations for the low femoral neck BMD in men include factors that may predispose the patients to both RA and low BMD, such as smoking and low androgen levels.[3] The increasing lumbar spine BMD could be due to more extensive antiosteoporotic treatment compared to the reference population, or could be the result of more artefacts, such as extensive aortic calcification or degenerative spinal changes, in patients with RA.

References

1. Rydholm M et al. Despite early improvement, patients with rheumatoid arthritis still have impaired grip force 5 years after diagnosis. Arthritis Care Res. 2018;70:491-8.
2. Rydell E et al. Smoking, body mass index, disease activity, and the risk of rapid radiographic progression in patients with early rheumatoid arthritis. Arthritis Res Ther. 2018;20:82.
3. Pikwer M et al. Association between testosterone levels and risk of future rheumatoid arthritis in men. Ann Rheum Dis. 2014;73(3):573-9.

Lower Back Pain Due to Enthesopathy of Erector Spine Muscle: A Comparative Ultrasound and MRI Study in Patients with Iliac Crest Pain Syndrome

Authors: *Plamen Todorov,[1] Rodina Nestorova,[2] Maria Kalcheva,[3] Anastas Batalov[1]

1. Rheumatology Department, Medical University of Plovdiv, Plovdiv, Bulgaria
2. Rheumatology Department, "St Irina" Medical Centre, Sofia, Bulgaria
3. Rusev Laboratories: Specialised Medical Imaging Laboratories, 5th Hospital, Sofia, Bulgaria

*Correspondence to drtodorovplamen@gmail.com

Disclosure: The authors have declared no conflicts of interest.

Keywords: Lower back pain, MRI, pain syndromes, ultrasound.

Citation: EMJ Rheumatol. 2018;5[1]:54-56. Abstract Review No. AR7.

BACKGROUND

Regional pain syndromes are thought to be caused by soft tissue pathologies and are a frequent cause of musculoskeletal complaints. One of these syndromes, namely iliac crest pain syndrome (ICPS), is particularly common in patients with lower back pain (LBP). It is characterised clinically by pain perceived maximally at the most medial part of the posterior iliac crest. In addition, patients should recognise the pain provoked by a systematic digital palpation in this area as 'their own' typical pain.[1] Though ICPS is very frequently encountered in LBP, the exact aetiology of this syndrome has not been established. Based on anatomical data, it was suggested that ICPS could be caused by a tendinopathy or enthesopathy of the erector spine (ES) muscle attachments to the medial iliac crest (MIC).[2] In a previous anatomical and ultrasound (US) study we showed that this might be the case.[3]

AIMS

The purpose of this study was to test the ability of US and MRI to identify pathological transformations in the ES muscle entheses at the MIC in patients with LBP. Furthermore, we calculated the sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV), and the overall accuracy of the US and MRI to diagnose ICPS alongside clinical assessment to determine the gold standard diagnostic technique.

METHODS

A total of 25 patients (9 men and 16 women with a mean age of 43.12±11.83 and mean BMI of 25.07±2.36) with anamnesis of chronic, nonspecific (after lateral X-ray and standard clinical examination) LBP perceived maximally in the region of the MIC unilaterally or bilaterally were included in the study. First, a systematic palpation of the posterior MIC bilaterally was performed by an independent examiner to diagnose ICPS clinically. Then, over 2 successive days, each patient underwent MRI examination of the lower back (lumbar and sacroiliac regions), with an enlarged field of view in the sagittal

plane, and a standardised US examination of the ES terminal tendons and entheses bilaterally (Figure 1).

The MRI data were assessed by a radiologist with 10 years of MRI experience. The sonographies were performed and analysed by a rheumatologist with 7 years of US experience and analysed in accordance with the OMERACT definition of enthesopathy.[4] Both the radiologist and the sonographer were blinded to the clinical findings of the given patient.

RESULTS

Clinical examination (palpation) identified 25 painful ES entheses of the total 50 cases examined, while MRI revealed pathology in 21 of the 50 ES entheses and US showed 27 of the 50 pathological ES entheses.

Based on these findings, the sensitivity, specificity, PPV, NPV, and overall accuracy of the US and the MRI for the assessment of ES entheses were calculated (at structure; i.e., an enthesis level) (Table 1).

CONCLUSION

This study shows that both US and MRI have good capability to identify pathological transformation in the ES entheses in patients with nonspecific LBP. US and MRI showed equal specificity but US had greater sensitivity. These diagnostic properties of US could be of value when assessing patients with otherwise nonspecific LBP, especially those likely to have soft tissue regional pain syndromes like ICPS.

DISCUSSION RAISED

Discussion at the presentation was about the fact that soft tissue rheumatic pain is frequently overlooked in patients with LBP, despite it being very common. It was also mentioned that a clinician should maintain their anatomy knowledge to be a good diagnostician.

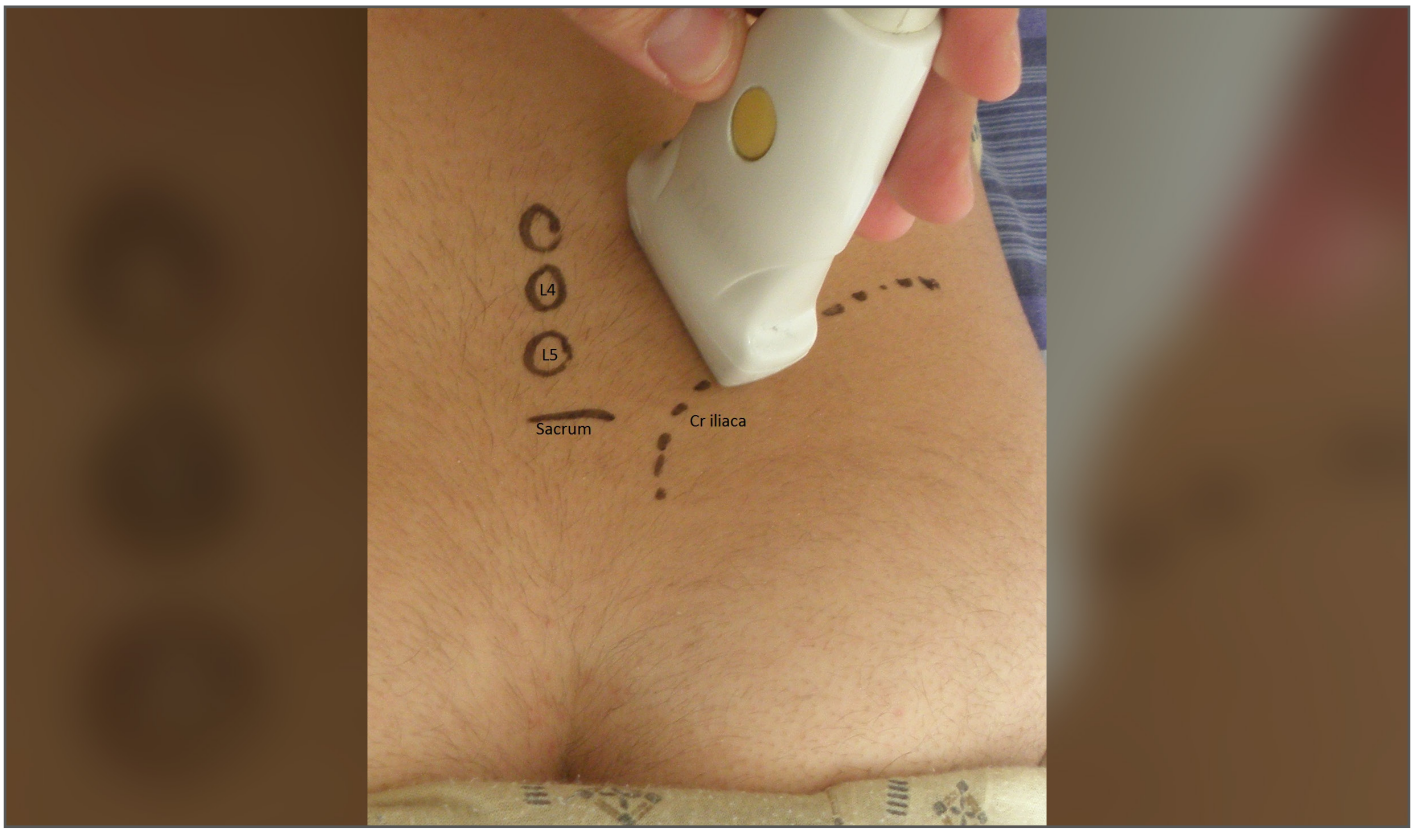


Figure 1: Position of the ultrasound probe for scanning of the right erector spine enthesis in the longitudinal plane (left side of the image is medial).

Table 1: Summary of the tests performed to compare ultrasound and MRI for the diagnosis of erector spine muscle entheses in patients with lower back pain.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
US	88% (69–97%)	80% (60–93%)	82% (67–91%)	87% (69–93%)	84% (71–93%)
MRI	64% (43–82%)	80% (59–93%)	76% (58–88%)	70% (56–80%)	71% (59–85%)

CI: confidence interval; NPV: negative predictive values; PPV: positive predictive values; US: ultrasound.

Finally, it was emphasised that this study opens the door for a new diagnostic application of musculoskeletal US, namely in patients with LBP of clinically unidentified origin.

References

1. Collee G et al. Iliac crest pain syndrome in low back pain: Frequency and features. J Rheumatol. 1991;18(7):1064-7.
2. Macintosh JE, Bogduk N. The attachments of the lumbar erector spinae. Spine (Phila Pa 1976). 1991;16(7):783-92.
3. Todorov P et al. The sonoanatomy of lumbar erector spinae and its iliac attachment - The potential substrate of the iliac crest pain syndrome, an ultrasound study in healthy subjects. J Ultrason. 2018;18(72):16-21.
4. Naredo E. Basic MSUS abnormalities definition (OMERACT) and appearance. Available at: http://www.aplar2016.com/wp-content/uploads/2016/10/Naredo_2_English.pdf. Last accessed: 10 July 2018.

The Diagnostic Journey of Patients with Ankylosing Spondylitis in the USA

Authors: *Alexis Ogdie,[1] W. Benjamin Nowell,[2] Regan Reynolds,[2] Kelly Gavigan,[2] Shilpa Venkatachalam,[2] Marie de la Cruz,[3] Emuella Flood,[3] Ethan J. Schwartz,[3] Beverly Romero,[3] Yujin Park[4]

1. Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA
2. Global Healthy Living Foundation, Upper Nyack, New York, USA
3. ICON, Gaithersburg, Maryland, USA
4. Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA

*Correspondence to alexis.ogdie@uphs.upenn.edu

Disclosure: Dr Ogdie has received consulting fees from Amgen, AbbVie, BMS, Celgene, Lilly, Novartis, Pfizer, and Takeda, and has received grant support from the National Institutes of Health (NIH)/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), Rheumatology Research Foundation, Pfizer, and Novartis. Dr Nowell, Ms Gavigan, and Dr Venkatachalam are employees of Global Healthy Living Foundation. Ms de la Cruz, Ms Flood, Ms Romero, and Mr Schwartz are employees of ICON Plc, which was contracted by Novartis to conduct this study. Dr Park is an employee of Novartis Pharmaceuticals Corporation. Ms Reynolds has declared no conflicts of interest.

Acknowledgements: This study was sponsored by Novartis Pharmaceuticals Corporation. Support for third-party writing assistance for this abstract review, furnished by Dr Paganelli and Dr Deutsch, Health Interactions, Inc., was provided by Novartis Pharmaceuticals Corporation. This work was partially supported through a Patient-Centered Outcomes Research Institute (PCORI) award (PPRN-1306-04811). All statements in this abstract review, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of PCORI, its Board of Governors, or the Methodology Committee.

Keywords: Ankylosing spondylitis (AS), CreakyJoints, patient diagnosis journey, sex differences, web-based survey.

Citation: EMJ Rheumatol. 2018;5[1]:56-58. Abstract Review No. AR8.

Ankylosing spondylitis (AS), a chronic inflammatory rheumatic disease characterised by inflammation of the sacroiliac joints and the spine,[1] has a reported prevalence between 0.2% and 0.5% in the USA.[2] However, the true prevalence of AS is unknown due to significant diagnosis delays and under-recognition of disease. A study based in the USA[3] demonstrated that patients with AS experience a significant delay (on average 14 years) from AS symptom onset to diagnosis. Understanding the diagnostic journey of patients with AS and identifying opportunities to quickly diagnose and appropriately refer patients is therefore critical to reducing time to diagnosis, preventing irreversible joint damage, and preserving mobility. This study aimed to describe the patient journey to AS diagnosis from the patient's perspective and identify sex differences via a web-based survey.

Adults from the USA aged ≥18 years with a self-reported diagnosis of AS were recruited through outreach on social media and using CreakyJoints, an online patient support community comprising patients with arthritis and arthritis-related diseases and their caregivers. Survey questions were developed following analysis of qualitative interviews of patients with AS and clinical experts, as well as a targeted literature review. Respondents completed a web-based survey on sociodemographics, clinical characteristics, diagnosis history, and impact of AS on work and relationships. Survey results were compared between women and men using the 2-sample T-test for continuous variables and a chi-squared test for categorical variables.

Among 235 respondents, 174 (74.0%) were women. On average, men were older than women (mean: 53.1 years [standard deviation (SD): 10.3] versus mean: 48.6 years [SD: 10.6], respectively); however, women had worse disease severity.

A

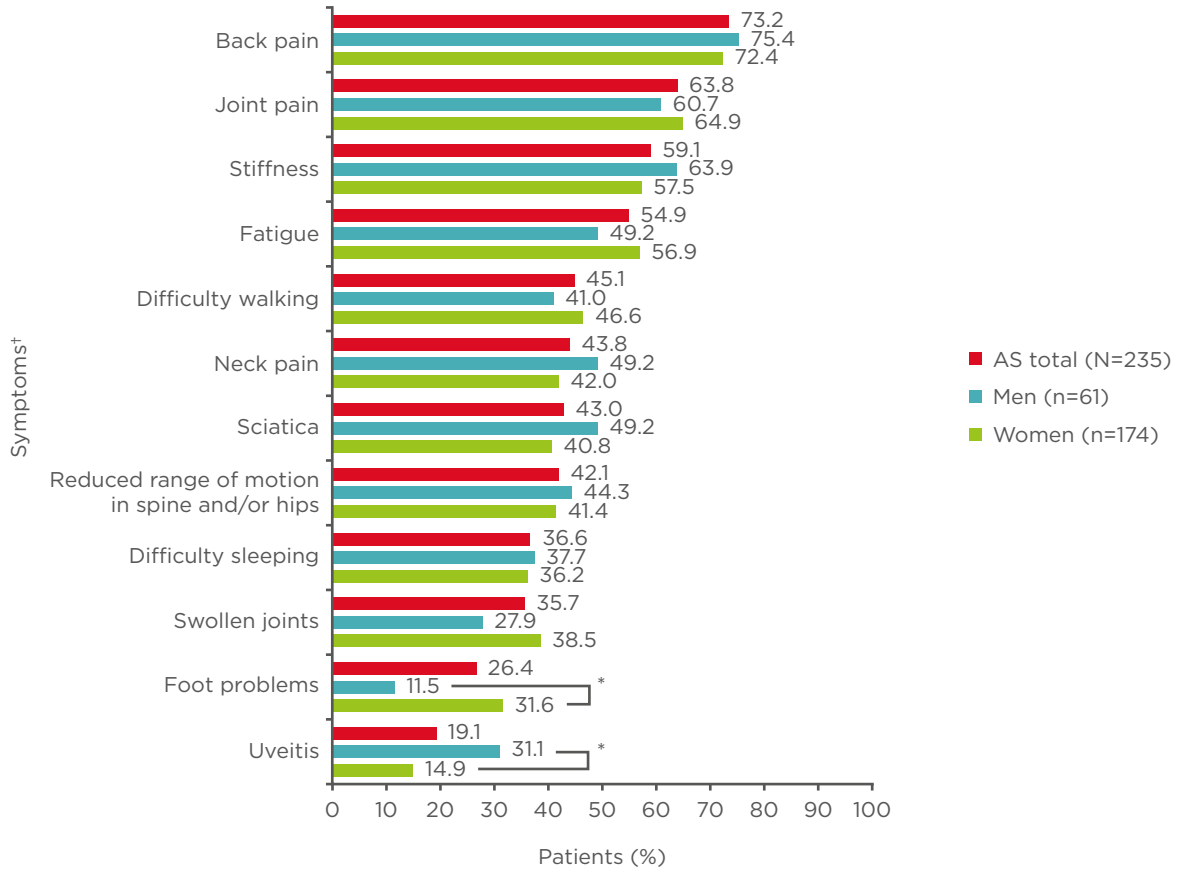


Figure 1A: The most common first symptoms in patients with ankylosing spondylitis to prompt seeking medical care.

*p<0.05 for comparisons between men and women; † Respondents were able to select >1 option.

AS: ankylosing spondylitis.

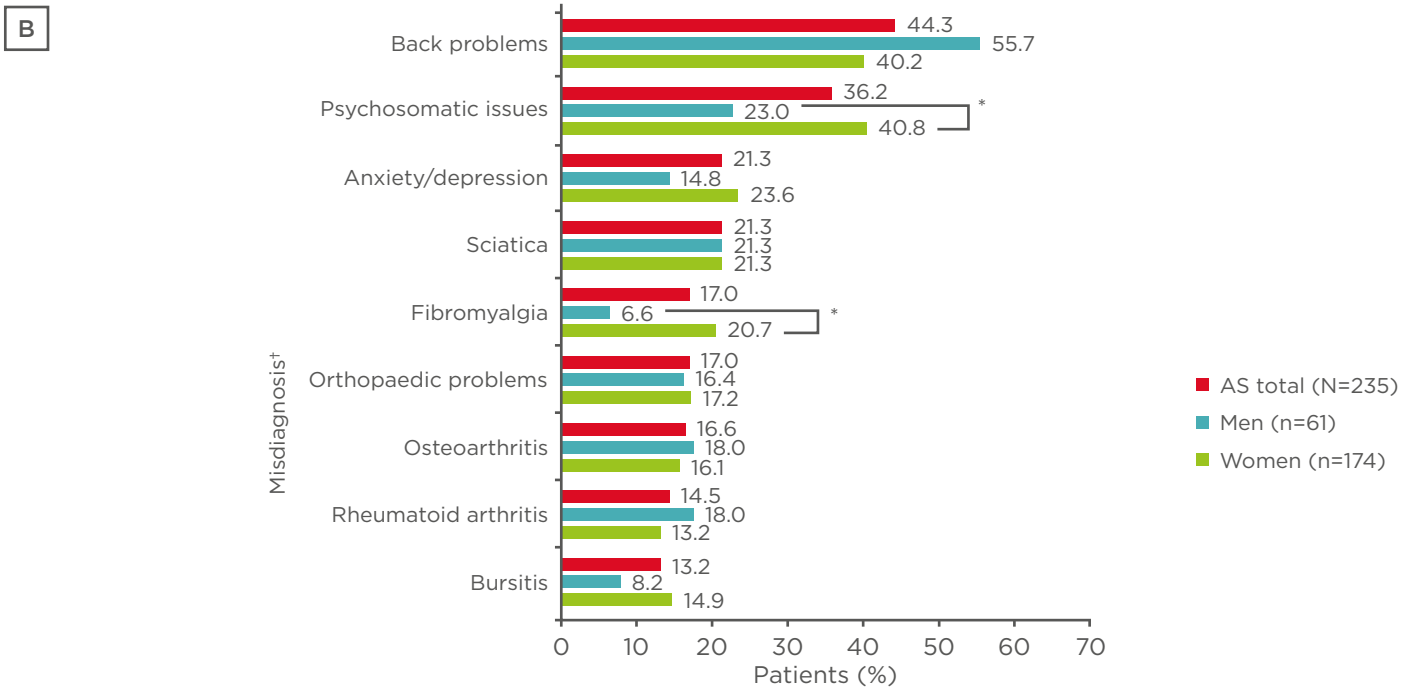


Figure 1B: The most common misdiagnoses in patients with ankylosing spondylitis.

*p<0.05 for comparisons between men and women; † Respondents were able to select >1 option.

AS: ankylosing spondylitis.

Overall, the mean time from symptom onset across all respondents was 17.9 years (SD: 12.6) and the mean time since official diagnosis was 8.5 years (SD: 9.3). The most common symptoms that led to seeking medical care were back pain, joint pain, stiffness, and fatigue (Figure 1A). Women were more likely than men to seek medical care due to foot problems (31.6% versus 11.5%, respectively), whereas men were more likely to seek care due to uveitis (31.1% versus 14.9%, respectively; both p<0.05). During diagnosis, respondents most commonly reported seeking medical care from a general practitioner (87.2%) and rheumatologist (65.1%), with no differences between women and men. The most commonly reported misdiagnoses were back problems (55.7%), psychosomatic issues (23.0%), and sciatica (21.3%) in men, whereas psychosomatic issues (40.8%), back problems (40.2%), and anxiety and depression (23.6%) were most common in women. Significantly higher proportions of women than men reported misdiagnoses of psychosomatic issues (40.8% versus 23.0%, respectively) and fibromyalgia (20.7% versus 6.6%, respectively) (Figure 1B). All respondents reported a significant impact of their AS on work and relationships, with women more likely to report an impact on aspects of their relationships than men.

These survey findings highlight differences between men and women in initial symptom presentation, misdiagnoses, time to diagnosis of AS, and impact of AS on work and relationships. Early recognition of symptoms associated with AS and understanding potential sex differences in symptom presentation over time will help reduce misdiagnoses and shorten the time to diagnosis of AS, leading to improved care and health-related quality of life.

References

1. Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007;369(9570):1379-90.
2. Reveille JD. Epidemiology of spondyloarthritis in North America. Am J Med Sci. 2011;341(4):284-6.
3. Deodhar A et al. Frequency of axial spondyloarthritis diagnosis among patients seen by US rheumatologists for evaluation of chronic back pain. Arthritis Rheumatol. 2016;68(7):1669-76.

JAK Inhibitors in the Treatment Algorithm of Rheumatoid Arthritis: A Review

EDITOR'S PICK

This excellent paper reviews the role of the JAK kinase pathway in inflammation and its potential as a therapeutic target for treating rheumatoid arthritis. Up to 30% of rheumatoid arthritis patients do not respond to treatment with monoclonal antibody drugs and some develop secondary efficacy failures. Thus, JAK inhibitors represent a revolutionary innovation for the treatment of inflammatory conditions, even beyond the field of rheumatology. Whilst these drugs remain expensive, the future is bright for this wonderful treatment modality, as this article demonstrates.

Dr Ian Chikanza

Barts and the Royal London Hospital, UK

Authors: Salvatore Bellinvia,[1] *Christopher J. Edwards[2]

1. Department of Rheumatology, Salisbury NHS Foundation Trust, Salisbury, UK
2. Department of Rheumatology and NIHR Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, UK

*Correspondence to cedwards@soton.ac.uk

Disclosure: Dr Edwards has received consultancy, research support, and speaker's bureau honoraria from Abbvie, Biogen, BMS, Celgene, Lilly, Mundipharma, Pfizer, Roche, MSD, Fresenius, Samsung, and UCB. Dr Bellinvia has declared no conflicts of interest.

Received: 13.03.18

Accepted: 31.05.18

Keywords: JAK inhibitors, rheumatoid arthritis (RA), targeted synthetic disease-modifying antirheumatic drugs (tsDMARD), treatment algorithm.

Citation: EMJ Rheumatol. 2018;5[1]:59-65.

Abstract

Biological disease-modifying antirheumatic drugs have defined a new era in rheumatoid arthritis (RA) management but share the limitation of antagonising single inflammatory cytokines or cells, as well as being either intravenously or subcutaneously administered. Following advances in the understanding of signalling pathways, the introduction of orally administered small molecules targeting key downstream intracellular factors constitutes a major breakthrough since the advent of biologics. JAK inhibition is a novel approach for treating RA and a series of agents directed against JAK have been developed for clinical use, paving the way for an innovative approach to treatment and the addition of a new class of targeted synthetic disease-modifying antirheumatic drugs to the available therapeutic armamentarium. Clinicians must now consider the place of these drugs in disease management. This review summarises the impact of JAK inhibitors and their role in the treatment algorithm of RA.

TREATMENT APPROACH IN RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder primarily affecting the synovial joints resulting in severe, progressive destruction of articular cartilage, subchondral bone, tendons, and ligaments. RA is the most common inflammatory arthritis, affecting 0.5–1.0% of the population worldwide.[1] If not promptly and successfully treated, the condition can lead to considerable loss of function and an inability to work, having a significant impact on an individual's quality of life and leading to an adverse social cost for the community. The last few decades have seen a dramatic change in the concept of treatment, from management strategies merely focussed on symptomatic relief and control to the adoption and implementation of a treat-to-target (T2T) approach related to the consistent measurement of disease activity in real-world clinical practice, rather than exclusively in the more formal setting of randomised clinical trials.[2] Formal T2T guidelines for RA were developed several years ago,[3] and similar principles based on the accurate quantification of remission or low disease activity achievement have been subsequently implemented for other rheumatic conditions.[4,5] In parallel, it has also been clearly demonstrated that intensive treatment initiated soon after diagnosis is able to prevent structural damage and disease progression and improve quality of life in comparison to late treatment initiation.[6-8] The benefits of early aggressive treatment of RA make up for the higher costs of medicinal products usually regarded as second-line treatment.[9] This is more in line with the primary therapeutic goals set by the T2T approach of achieving remission or low disease activity, as well as having clear social benefits in terms of work impairment and quality of life.

BIOLOGICAL DISEASE-MODIFYING ANTIRHEUMATIC DRUGS FOR RHEUMATOID ARTHRITIS

In the late 1990s, the huge advances in the understanding of the cells and mediators involved in the pathogenic process of RA, specifically the role of cytokines as proinflammatory agents directly responsible for symptoms and articular damage,[10] allowed for major changes in the management of the disease through the introduction of biologic agents. TNF inhibitors (TNFi) were the first biologic drugs to be licensed for RA; since then, a multitude of other single-cytokine-targeting biological agents have been approved for use. Other available biologics use a different mode of action to cytokine inhibitors, antagonising B cell function or T cell costimulation. These macromolecular proteins have markedly changed disease management and improved prognosis and outcomes in RA but, nevertheless, have also presented clinicians and budget decision-makers with challenges, with rheumatologists being at the forefront in this changing landscape.[11] Although biologics can be superior to conventional synthetic disease-modifying antirheumatic drugs (csDMARD), in many situations, unresponsiveness to treatment is still an ongoing issue, and primary or secondary non-response continues to be seen in up to 40% of patients.[12] Moreover, the availability of biologics has been compromised by the reality of high treatment costs. This has limited their wider adoption and restricted their use as a second-line therapy if the treatment target is not achieved with the first csDMARD strategy. The need to reduce costs has led to the successful introduction of biosimilar drugs with the expiration of patent protection for TNFi originators, and this has been greeted with enthusiasm by budget policymakers but not by all clinicians and rheumatology national societies and organisations, as highlighted by several position statements released over the last few years.[13-16] Furthermore, while the high effectiveness of biologics has been described both in randomised controlled trials and real-world data, several studies over the last few years have demonstrated high discontinuation rates with biologics, with side effects and a lack of efficacy being among the main causes for treatment cessation.[17] The route of administration, either intravenously or via subcutaneous self-injections, can play a role in predisposing patients to discontinue their biologics, especially in the first month of therapy,[18] and implementation of regular follow-up programmes to ensure long-term adherence, in its various aspects of regularity and continuity, presents clinicians with a number of obstacles. To date, several biological agents have been

licensed for use in RA, more recently followed by approval of targeted synthetic DMARD (tsDMARD), oral small molecules that block JAK, thereby inhibiting the signalling pathway.

JAK: SINGLE TARGET VERSUS A GROUP OF TARGETS

The selective inhibition of a single cytokine or cell by antagonising receptor binding on a cell surface level has not always proven satisfactory in achieving disease control in RA, perhaps because a remarkable array of multiple cytokines have been described as being important in its pathogenesis. Therefore, the logical consequence of recent advances in the understanding of downstream signalling pathways has been the development of new therapeutic agents that can provide effects across several cytokines.[19] JAK are a group of four intracellular enzymes (JAK1, JAK2, JAK3, and TYK2) belonging to the larger family of tyrosine kinases. JAK proteins are constitutively bound to the cytoplasmic tail of cell surface receptors and transduce signals from a wealth of cytokines by phosphorylation of STAT factors that subsequently translocate into the nucleus, where they regulate gene expression. Multiple STAT factors have been implicated in the expression of many proinflammatory genes and are expressed in the synovial tissue of patients with RA. STAT activation correlates with disease activity in RA, demonstrating that this signalling pathway is specifically important for disease pathogenesis.[20] There is increasing evidence coupling the specific JAK proteins to individual cytokine responses, although there is not yet a comprehensive and detailed description of these mechanisms (Table 1). The essential role of JAK1/3 in mediating signal transduction of IL-2, 4, 7, 9, 15, and 21 has been demonstrated, while JAK1/2 is involved in IFN-γ and IL-6 pathways. In contrast to these, the JAK2/2 homodimer has critical implications for erythropoiesis and thrombopoiesis, and mutations are notoriously associated with acute and chronic haematologic malignancies. TYK2 plays an important role in the IL-12/IL-23 pathway. Loss of their function in knockout mice has proven to lead to a phenotype of severe combined immune deficiency, defective lymphopoiesis, and erythropoiesis, supporting the potential role of JAK inhibitors as immunomodulators.[21,22] In the field of kinase inhibitors, much of our knowledge is derived from oncology, based on the finding that enhanced JAK activity has been revealed in several myeloproliferative diseases. This is not the first time rheumatologists have taken and used medications from oncology. In this sense, the advent of JAK inhibitors has meant going 'back to the future',[23] providing the opportunity to switch off a group of inflammatory pathways in RA, thus moving beyond the concept established with biologics of targeting single inflammatory cytokine or cell functions.

Table 1: JAK heterodimers and homodimers important for the signalling of particular cytokines.

Cytokines		IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	EPO, TPO, GH	IL-3, IL-5, GM-CSF	IL-13, IL-6	IL-12, IL-23	Type 1 IFN (α/β)	Type 2 IFN (γ)
JAK heterodimers and homodimers*		JAK1 JAK3	JAK2 JAK3	JAK2 JAK2	JAK1 TYK2 JAK2	JAK2 TYK2	JAK1 TYK2	JAK1 JAK2
Inhibition†	JAK1	+	-	-	+	-	+	+
	JAK2	-	+	+	+	+	-	+
	JAK3	+	-	-	-	-	-	-
	TYK2	-	-	-	+	+	+	-

*Different cytokines signal through different JAK combinations. †To inhibit the signalling initiated by these cytokines, particular JAK must be inhibited. This gives opportunities to design specific JAK inhibitors that reduce signaling from particular cytokines.

EPO: erythropoietin; GH: growth hormone; GM-CSF: granulocyte-macrophage colony-stimulating factor; TPO: thrombopoietin.

JAK INHIBITORS IN RHEUMATOID ARTHRITIS

The introduction of oral, small molecule JAK inhibitors (also known as jakinibs) has added a new class of tsDMARD to the available rheumatologic therapeutic armamentarium. Tofacitinib was the first JAK inhibitor to be tested in humans and was granted U.S. Food and Drug Administration (FDA) approval for the treatment of moderately-to-severely active RA in 2012. The European Medicines Agency (EMA) initially refused an application for clinical use of tofacitinib in 2013, but this tsDMARD finally received EMA approval in 2017. Tofacitinib is an oral, reversible, pan-JAK inhibitor, initially designed to be a specific inhibitor of JAK3 but then found to inhibit the kinase activity of JAK1, as well as having a small effect on JAK2 and TYK2. Tofacitinib and methotrexate in combination therapy was non-inferior to adalimumab and methotrexate in the treatment of RA in a non-inferiority, head-to-head, randomised controlled trial in patients with an inadequate response to methotrexate, without major safety concerns.[24] From a clinically relevant and practical perspective, the results of this study suggested that, in patients with an inadequate response to methotrexate, the addition of tofacitinib or adalimumab was equally effective, while switching to tofacitinib monotherapy failed to achieve non-inferiority to either combination therapy. The rate of adverse events, with particular regard to those of special interest, including serious infections and malignancies, was similar between the treatment groups. Despite previous assumptions about an increased rate of herpes zoster in patients receiving tofacitinib compared to biologic-treated patients,[25] the incidence was similar across all the three groups, although a possible channelling bias was acknowledged because patients at higher risk might have been more likely to receive a vaccine. A mild, but statistically significant, increase in high density lipoproteins and low density lipoproteins has also been described in clinical trials.[24] Limited changes in neutrophil count, lymphocyte count, and haemoglobin levels were seen with tofacitinib treatment, but these stabilised over time in long-term extension studies, with clinically meaningful reductions in haemoglobin levels occurring in <1% of patients in all treatment groups.[26]

Baricitinib is an orally available, reversible JAK inhibitor with specificity for JAK1 over JAK2 and was also granted EMA approval in 2017, a few months before tofacitinib, therefore being the first JAK inhibitor approved to treat RA in the European Union (EU). The FDA was initially unable to approve the application, indicating additional data were needed to determine the most appropriate doses and to further characterise safety concerns. A resubmission to the FDA had to be filed and the manufacturer has finally announced FDA approval of the 2 mg dose of baricitinib on June 1, 2018. In a randomised, double-blind, placebo and active-controlled trial of patients who had an inadequate response to methotrexate (the RA-BEAM study),[27] baricitinib was associated with significant clinical improvements compared with placebo and adalimumab. Of note, an increased American College of Rheumatology (ACR)20 score response rate at Week 12 was noted with baricitinib versus adalimumab (70% and 61%, respectively). Furthermore, baricitinib was found to be superior to adalimumab in the mean Disease Activity Score 28-joint count C reactive protein change achieved at Week 12. Rates of adverse events were similar with baricitinib and adalimumab, including serious infections. As for haematological abnormalities, baricitinib was associated with a reduction in neutrophil count, early transient increases in lymphocyte count, and modest increases in platelet count.

The pursuit of more selective therapies, particularly aiming to minimise inhibition of JAK2 and the alleged impact on haemoglobin, lymphocyte, and neutrophil counts, has focussed efforts on the development of JAK1 and JAK3 selective inhibitors. For example, filgotinib is highly specific for JAK1 and has demonstrated clinical efficacy and safety as an add-on treatment to methotrexate in patients with an insufficient response to methotrexate (DARWIN 1),[28] as well as proving effective as a monotherapy, with a rapid onset of action (DARWIN 2).[29]

Upadacitinib, a selective inhibitor of JAK1 in development for the treatment of adult patients with moderately-to-severely active RA, has been investigated with background methotrexate in patients who had failed at least one TNFi biologic therapy (BALANCE I) and in a companion broad dose-range study comparing

the efficacy and safety of upadacitinib versus placebo in patients with an inadequate response to methotrexate (BALANCE II).[30,31] The safety and tolerability profiles in these Phase II studies were similar to other JAK inhibitors without obvious improved benefit-risk profiles. Results from larger Phase III trials (the robust SELECT programme) have been recently announced that showed positive results and met the primary endpoints as a monotherapy, also in patients with an inadequate response to methotrexate.[32] The safety profile of upadacitinib was consistent with previously reported Phase II studies and no new safety signals were detected.

Peficitinib and decernotinib are novel selective inhibitors of JAK3 that have been shown to be effective in reducing signs and symptoms of RA and obtaining significant ACR score response rates in patients with a prior inadequate response to conventional synthetic DMARD, with limited emerging safety signals.[33-35] Overall, a characteristic class safety profile is taking shape for JAK inhibitors,[36] although differences among individual agents might emerge based on their selectivity. A higher risk of herpes zoster infection with most JAK inhibitors, compared to that associated with biological therapies, has been shown in real-world analysis and extension studies, thus revealing a likely class effect. However, long-term follow-up studies are necessary to assess whether JAK inhibitors are associated with an increased risk of malignancy, for instance.

JAK INHIBITORS IN THE TREATMENT ALGORITHM OF RHEUMATOID ARTHRITIS

JAK inhibitors represent a major addition to the rheumatology field and their development has expanded the number of therapeutic tools available to patients and clinicians, with a relevant impact on the treatment algorithm of RA and the guidelines endorsed by international bodies. However, recommendations vary on the optimal treatment following an inadequate response to conventional DMARD. Current European League Against Rheumatism (EULAR) guidelines for the management of RA[37] recommend the addition of a biological DMARD or a tsDMARD if the treatment target is not achieved with the first csDMARD strategy and poor prognostic factors are present, although a slight preference is given to biologics over targeted synthetic drugs due to the availability of long-term safety data. This approach was also previously used in justifying the use of TNFi as the preferred first-line biologic therapy over other biological therapies due to a long-term evidence base and the availability of registry data concerning efficacy and safety.

The 2015 ACR guideline for the treatment of RA[38] included tofacitinib alone as the only FDA-approved JAK inhibitor and concluded that the use of combination traditional DMARD or addition of a TNFi, a non-TNF biologic, or tofacitinib is recommended for patients with established RA with moderate or high disease activity despite DMARD monotherapy, without focussing on prognostic factors or expressing any preferences. The limited direct comparative evidence for these therapies in this clinical situation has precluded the recommendation of ranking these treatment options. In recent years, increasing interest has been shown in developing head-to-head designed studies comparing JAK inhibitors and biological products with early signs of significant differences in clinical endpoints.[27] These first signals are encouraging for the use of JAK inhibitors, but it remains to be seen whether this will sanction the superiority of a mechanism of action in the long-term.

The focus on patient involvement in treatment decisions has gained a central role in current RA T2T strategies. With the advent of orally available products, this concept will need further and greater consideration in informing and updating current recommendations for selection of the optimal treatment in the setting of an inadequate response to first DMARD combination therapy. With the recent licensing for use in RA, oral targeted therapy with JAK inhibitors is now a reality, and the ease of use of an oral therapy may promote these medications to the second-line therapy of choice in the treatment algorithm of RA. In parts of the world where there is a difficulty ensuring a cold supply chain, oral therapies may also provide some advantages.

ECONOMIC CONSIDERATIONS

The economic impact of JAK inhibitors will also play a crucial role in their dissemination, as the

preferential use of the least expensive therapy among treatments with similar efficacy and safety profiles is a recognised benchmark widely adopted by healthcare decision-makers at a local level. Negotiated procurement discounts for available JAK inhibitors are often provided, aiming for a cost burden close to that of biosimilars. Currently, there are limited data evaluating the expenditure of an RA treatment strategy including JAK inhibitors, although budget impact analyses, carried out in the USA where tofacitinib has been available for longer, have been encouraging, showing limited additional costs or even potential cost savings.[39,40] Furthermore, with the expiration of patent protection for JAK inhibitors, we may also witness the successful introduction of medicinal products leading to even more considerable positive outcomes on budget to that achieved with biosimilars.

CONCLUSION

JAK inhibitors are novel, orally administered, effective, and rapidly acting agents for the treatment of RA. The introduction of the first non-selective JAK inhibitors constitutes a major breakthrough since the advent of biologics, overcoming the limitations of antagonising a single target through a broader magnitude of response. The oral route of administration of JAK inhibitors has the potential to minimise drug discontinuation, in contrast with parentally administered biological products. To date, international recommendations have carefully avoided expressing a definite ranking of these treatment options, but further head-to-head comparative studies may undermine this approach. The choice of the optimal treatment of active disease after inadequate response to conventional DMARD should be made by physicians through a shared decision-making process, and patients' values and preferences could play a major role in this increasingly hot spot in the treatment algorithm of RA.

References

1. Humphreys JH et al. The incidence of rheumatoid arthritis in the UK: Comparisons using the 2010 ACR/EULAR classification criteria and the 1987 ACR classification criteria. Results from the Norfolk Arthritis Register. Ann Rheum Dis. 2013;72(8):1315-20.
2. Cohen MD, Keystone EC. Rational therapy in RA: Issues in implementing a treat-to-target approach in RA. Nat Rev Rheumatol. 2013;9(3):137-8.
3. Smolen JS et al. Treating rheumatoid arthritis to target: Recommendations of an international task force. Ann Rheum Dis. 2010;69(4):631-7.
4. van Vollenhoven RF et al. Treat-to-target in systemic lupus erythematosus: Recommendations from an international task force. Ann Rheum Dis. 2014;73(6):958-67.
5. Smolen JS et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis. 2017;77(1):3-17.
6. Combe B. Early rheumatoid arthritis: Strategies for prevention and management. Best Pract Res Clin Rheumatol. 2007;21(1):27-42.
7. Emery P et al. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: A two-year, double-blind, randomized study. Arthritis Rheum. 2010;62(3):674-82.
8. Emery P et al. A European chart review study on early rheumatoid arthritis treatment patterns, clinical outcomes, and healthcare utilization. Rheumatol Int. 2015;35(11):1837-49.
9. Jansen JP et al. Cost-effectiveness of sequenced treatment of rheumatoid arthritis with targeted immune modulators. J Med Econ. 2017;20(7):703-14.
10. Avramescu C et al. Cytokinic panel in rheumatoid arthritis and correlation with histological patterns of synovitis -- Active type of disease. Rom J Morphol and Embryol. 2005;46(2): 87-92.
11. Dörner T et al. The changing landscape of biosimilars in rheumatology. Ann Rheum Dis. 2016;75(6):974-82.
12. Listing J et al. Clinical and functional remission: Even though biologics are superior to conventional DMARDs overall success rates remain low– Results from RABBIT, the German biologics register. Arthritis Res Ther. 2006;8:R66.
13. Fiorino G et al. The use of biosimilars in immune-mediated disease: A joint Italian Society of Rheumatology (SIR), Italian Society of Dermatology (SIDeMaST), and Italian Group of Inflammatory Bowel Disease (IG-IBD) position paper. Autoimmun Rev. 2014;13(7):751-5.
14. Argüelles-Arias F et al. Joint position statement by "Sociedad Española de Patología Digestiva" (Spanish Society of Gastroenterology) and "Sociedad Española de Farmacología" (Spanish Society of Pharmacology) on biosimilar therapy for inflammatory bowel disease. Rev Esp Enferm Dig. 2013;105(1):37-43.
15. Fonseca JE et al. The Portuguese Society of Rheumatology position paper on the use of biosimilars. Acta Reumatol Port. 2014;39(1):60-71.
16. American College of Rheumatology. Position statement on biosimilars. Available at: https://www.rheumatology.org/Portals/0/Files/Biosimilars-Position-Statement.pdf. Last accessed: 23 May 2018.
17. Garcia-Gonzalez A et al. Treatment adherence in patients with

rheumatoid arthritis and systemic lupus erythematosus. Clin Rheumatol. 2008;27(7):883-9.

18. Betegnie AL et al. Why do patients with chronic inflammatory rheumatic diseases discontinue their biologics? An assessment of patients' adherence using a self-report questionnaire. J Rheumatol. 2016;43(4):724-30.
19. Smolen JS, Aletaha D. Rheumatoid arthritis therapy reappraisal: Strategies, opportunities and challenges. Nat Rev Rheumatol. 2015;11:276-89.
20. Firestein GS, "Etiology and pathogenesis of rheumatoid arthritis," Firestein GS et al. (eds.), Kelley's Textbook of Rheumatology (2013), Philadelphia, pp.1095-6.
21. O'Shea JJ et al. The JAK-STAT pathway: Impact on human disease and therapeutic intervention. Annu Rev Med. 2015;66:311-28.
22. MacFarlane LA, Todd DJ. Kinase inhibitors: The next generation of therapies in the treatment of rheumatoid arthritis. Int J Rheum Dis. 2014;17(4):359-68.
23. O'Shea JJ et al. Back to the future: Oral targeted therapy for RA and other autoimmune diseases. Nat Rev Rheumatol. 2013;9(3):173-82.
24. Fleischmann R et al.; ORAL strategy investigators. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): A Phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet. 2017;390(10093):457-68.
25. Curtis JR et al. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis. 2016;75(10):1843-7.
26. Schulze-Koops H et al. Analysis of haematological changes in tofacitinib-treated patients with rheumatoid arthritis across Phase 3 and long-term extension studies. Rheumatology (Oxford). 2017;56(1):46-57.
27. Taylor PC et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med. 2017;376(7):652-62.
28. Westhovens R et al. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: Results from a randomised, dose-finding study (DARWIN 1). Ann Rheum Dis. 2017;76(6):998-1008.
29. Kavanaugh A et al. Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: Results from a randomised, dose-finding study (DARWIN 2). Ann Rheum Dis. 2017;76(6):1009-19.
30. Kremer JM et al. A Phase IIb study of ABT-494, a selective JAK-1 inhibitor, in patients with rheumatoid arthritis and an inadequate response to anti-tumor necrosis factor therapy. Arthritis Rheumatol. 2016;68(12):2867-77.
31. Genovese MC et al. Efficacy and safety of ABT-494, a selective JAK-1 inhibitor, in a Phase IIb study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Rheumatol. 2016;68(12):2857-66.
32. AbbVie. AbbVie's upadacitinib shows positive results as monotherapy in Phase 3 rheumatoid arthritis study, meeting all primary and key secondary endpoints. 2017. Available at: https://news.abbvie.com/news/abbvies-upadacitinib-shows-positive-results-as-monotherapy-in-phase-3-rheumatoid-arthritis-study-meeting-all-primary-and-key-secondary-endpoints.htm. Last accessed: 11 June 2018.
33. Genovese MC et al. Peficitinib, a JAK inhibitor, in combination with limited conventional synthetic disease-modifying antirheumatic drugs in the treatment of moderate-to-severe rheumatoid arthritis. Arthritis Rheumatol. 2017;69(5):932-42.
34. Kivitz AJ et al. Peficitinib, a JAK inhibitor, in the treatment of moderate-to-severe rheumatoid arthritis in patients with an inadequate response to methotrexate. Arthritis Rheumatol. 2017;69(4):709-19.
35. Fleischmann RM et al. A randomized, double-blind, placebo-controlled, twelve-week, dose-ranging study of decernotinib, an oral selective JAK-3 inhibitor, as monotherapy in patients with active rheumatoid arthritis. Arthritis Rheumatol. 2015;67(2):334-43.
36. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol. 2017;13(5):320.
37. Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76(6):960-77.
38. Singh JA et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68(1):1-26.
39. Claxton L et al. An economic evaluation of tofacitinib treatment in rheumatoid arthritis: Modeling the cost of treatment strategies in the United States. J Manag Care Spec Pharm. 2016;22(9):1088-102.
40. Bhattacharya R, Kamal KM. Budget impact analysis of tofacitinib for treatment of rheumatoid arthritis. J Arthritis. 2015;4:152.

Switching to Biosimilars in Inflammatory Rheumatic Conditions: Current Knowledge

Authors: *Filipe C. Araújo,[1,2] Joao Eurico Fonseca,[3,4] Joao Goncalves,[5]

1. Rheumatology and Osteoporosis Unit, Hospital de Sant'Ana, SCML, Portugal
2. Institute of Microbiology, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal
3. Rheumatology Research Unit, Faculty of Medicine, University of Lisbon, Lisbon, Portugal
4. Rheumatology and Metabolic Bone Diseases Department, Hospital de Santa Maria, Lisbon Academic Medical Centre, Lisbon, Portugal
5. Research Institute for Medicines (iMed), Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal

*Correspondence to flipar@msn.com

Disclosure: Dr Araújo has received consultant and speaker fees from Pfizer, Biogen, and MSD. Dr Fonseca has received unrestricted research grants or acted as a speaker for Abbvie, Amgen, BMS, Celltrion, Celgene, Hospira, Janssen, Lilly, MSD, Mundipharma, Novartis, Novo Nordisk, Pfizer, Roche, Servier, and UCB. Dr Goncalves has received fees from Pfizer, Merck, Abbvie, Roche, Celltrion, and Sandoz. This manuscript was neither sponsored nor financially supported.

Received: 19.03.18

Accepted: 05.06.18

Keywords: Biosimilar, immunogenicity, interchangeability, non-medical switch, rheumatoid arthritis (RA), rheumatic disease.

Citation: EMJ Rheumatol. 2018;5[1]:66-74.

Abstract

Biosimilars are more affordable versions of previously approved biopharmaceuticals that are designed to reduce healthcare expenditure and increase patient access to this therapeutic class. To achieve their economic potential, many European countries have started to switch patients from reference drugs to biosimilars. The purpose of this article is to provide a comprehensive perspective on the biosimilar switching controversy, to assess interchangeability regulation and switching policies, and to review current evidence on switching and immunogenicity in the context of inflammatory rheumatic conditions. Patients and physicians feel uncertain about switching highly complex and difficult-to-replicate biosimilars of monoclonal antibodies due to a theoretical risk of increased immunogenicity, especially in extrapolated indications and in a multiple switch scenario involving various biosimilars. However, past experience with smaller biosimilars (somatropin, filgrastim, epoetin), the high standards required for approval of biosimilars of monoclonal antibodies in the European market, and current evidence on switching to infliximab and etanercept biosimilars (especially CT-P13 and SB4) are reassuring. Furthermore, no increased immunogenicity has been reported after switching to biosimilars. Decisions on switching and interchangeability are not covered by the European Medical Agency (EMA) guidelines and are left to individual European states, as opposed to the U.S. Food and Drug Administration (FDA), which has set standards to assess interchangeability. In summary, current knowledge is in favour of switching to biosimilars but the authors consider that this should be a physician-led decision with the active contribution of patients and hospital pharmacists to the pharmacovigilance chain.

INTRODUCTION

Biosimilars are similar and more affordable versions of previously approved biopharmaceuticals entering the market after loss of patent exclusivity. They present no clinical benefit over the originators and their use is aimed at reducing healthcare expenditure and improvement of patient access. In Europe, they are expected to mitigate access inequities between Eastern, Northern, and Western countries, the former having fewer reimbursed biologicals and prices that far exceeded the countries' gross domestic product (GDP).[1] The first biosimilar for the treatment of inflammatory conditions was approved in 2013 by the European Medicines Agency (EMA)[2] and since then others have followed. However, biosimilar uptake has been slow and heterogeneous among European countries.[3] Drivers for penetration of biosimilars include market dynamics, incentive policies (such as quotas), and price discounts. One important driver is non-medical switching from a reference drug to a biosimilar, determined by country-level policies. A non-medical switch occurs when a biopharmaceutical is replaced by another for reasons not related to efficacy or safety (usually economic). To fully achieve the cost-saving potential of biosimilars, many European countries have started switching patients to biosimilar drugs.

This article will explore the reasons behind biosimilar switching controversies, as well as review regulations on interchangeability, current switching data, and immunogenicity in the treatment of inflammatory rheumatic diseases.

WHY IS BIOSIMILAR SWITCHING AN ISSUE?

Switching from a reference biopharmaceutical to a biosimilar in a patient with an inflammatory condition is still a matter of debate. Biotechnological drugs are generated from living organisms and have inherently variable high-order structures (secondary, tertiary, and quaternary folding) and post-translational modifications (such as glycosylation, disulphide bond formation, or amidation) that impact structure, function, and immunogenicity. For these reasons, it is not possible to replicate a biopharmaceutical as an exact copy of the reference product, rendering biosimilars similar but not identical to their originators.[4] Biosimilar manufacturers are required to follow regulatory standards to ensure that this expected variability remains within prespecified ranges.[5] Developing a biosimilar candidate is both complex and laborious and typically involves characterising critical quality attributes and reverse-engineer manufacturing of reference product (cell culture, upstream, harvest, and downstream processes). Each one of these steps may introduce unwanted variability, and therefore manufacturers must apply state-of-the-art bioanalytical assays and confirmatory clinical trials to ensure maximal similarity of the end product.[6]

Biosimilars were first introduced in the European market following approval of Omnitrope® (Sandoz, Holzkirchen, Germany), the biosimilar of somatropin (human growth hormone), in 2006. Until 2013, all licensed biosimilars were either hormone (somatropin) or glycoprotein (filgrastim, epoetin alfa, and zeta) analogues.[7] The first biosimilar of the monoclonal antibody infliximab was granted marketing authorisation in 2013[2] and, since then, biosimilars of etanercept, rituximab, adalimumab, and new biosimilars of infliximab were approved.[7]

Prospective and retrospective data have shown no significant safety or efficacy discrepancies following switch from reference to biosimilar hormones or glycoproteins. Somatropin, for instance, has the longest post-approval period and substantial cumulative data that revealed no unexpected adverse events and sustained efficacy in extrapolated indications and after switch.[8,9] Filgrastim and complex glycoproteins, like epoetin alfa and epoetin zeta, have shorter post-approval periods but larger numbers of treated patients, and no difference in relevant clinical outcomes after switch.[10,11]

Notwithstanding this favourable historical background, switching biosimilars in the context of chronic inflammatory conditions has found resistance among patients and physicians due to concerns attributable mostly to immunogenicity.[12-14] The rationale is that monoclonal antibodies and fusion proteins are much more difficult to replicate and may be more susceptible to immunogenic reactions. They have incommensurably more

complex high-order structures and post-translational modifications, reaching close to 150 kDa of molecular weight compared to 30–40 kDa of hormones or glycoproteins.[6] Furthermore, immunogenicity may be elicited not only from protein structure and post-translational modifications, but may also be process-related (impurities, aggregates, formulation, and storage conditions).

An immunogenic reaction characterised by anti-drug antibody (ADA) production is expected when two antigenically distinct proteins are switched. By definition, biosimilars must be antigenically similar to their originators. As depicted later in this paper, the majority of approved biosimilars in regulated markets have pre and post-approval studies confirming no increased immunogenicity after one or just a few switches, performed in monitored clinical settings; however, a scenario not tested is multiple switches between biosimilars. All biosimilars are tested against their reference product and may have minor differences in physicochemical or biological properties that have no impact on efficacy, safety, or immunogenicity. In upcoming years, there will be various biosimilar versions of the same reference product in the market and these may be used interchangeably as instructed by government authorities or hospital administrations. Considering that biosimilars are not required to demonstrate similarity amongst themselves and that numerous manufacturing changes occur throughout their life cycle, there is a theoretical risk that two biosimilars of the same reference product may diverge and become molecules with significant structural variations.[15] Repeated exposure to such molecules with different stabilities or aggregation behaviour may increase the risk of immunogenic reactions with deleterious consequences for safety and efficacy.

Another concern, aside from immunogenicity, relates to pharmacokinetics (PK) and pharmacodynamics. All approved biosimilars have demonstrated a similar PK and, when available and relevant, pharmacodynamic profiles of their reference drug in a Phase I clinical trial.[5] This is particularly important for large proteins such as monoclonal antibodies that may have variable PK behaviour even within the same disease population.[4] When we consider scenarios that are not contemplated during the clinical assessment of a biosimilar candidate, patients and physicians feel uncertain. In a real-life setting, for instance, in which patients have several comorbidities and are treated with multiple concurrent drugs, there is a theoretical but remote risk that a biosimilar may behave differently from its reference drug, especially considering a disease condition for which no clinical studies were performed (extrapolated indication) and a multiple switch scenario.

Table 1: Position of rheumatology societies from European countries on biosimilar switching, interchangeability, and automatic substitution.

	Biosimilarity	Non-medical switch	Interchangeability	Automatic substitution
British Society for Rheumatology[22]	✓	✓	×	×
Italian Society of Rheumatology[23]	✓	✓	×	×
German Rheumatism League[24]	✓	×	×	×
Spanish Society of Rheumatology[25]	✓	✓	×	×
Portuguese Society of Rheumatology[26]	✓	✓	×	×
French Society for Rheumatology[27]	✓	✓	×	×
Royal Belgium Society for Rheumatology[28]	✓	×	×	×
Finnish Society for Rheumatology[29]	✓	✓	×	×

Green: acceptance; red: non-acceptance.

REGULATION ON INTERCHANGEABILITY AND BIOSIMILAR SWITCHING POLICIES

The only regulatory agency with available guidance on interchangeability is the U.S. Food and Drug Administration (FDA).[16] The Biologics Price Competition and Innovation Act (BPCIA) of 2009 distinguishes biosimilarity from interchangeability, stating that an interchangeable product must prove biosimilarity but is required to undergo further testing to demonstrate no risk to safety or efficacy of switching back and forth with the reference product.[17] To comply with this legal requirement, the FDA published 'Considerations in Demonstrating Interchangeability With a Reference Product - Guidance for Industry'[16] in January 2017 so that manufacturers could apply and have their biosimilars additionally licenced as interchangeable. This extensive draft guidance provides an overview on scientific considerations in demonstrating interchangeability, including data and information needed to support a demonstration of interchangeability; design and analysis of a switching study or studies; recommendations regarding the use of a USA-licensed reference product in a switching study or studies; and considerations for developing presentations, container closure systems, and delivery device constituent parts for proposed interchangeable products.[16] Furthermore, the BPCIA stated that once a biosimilar is licenced as interchangeable, pharmacy-level substitution may occur, meaning that a reference biopharmaceutical may be substituted at the pharmacy to the interchangeable version without the prescriber's consent.[17] The additional amount of data required to apply for a licence as an interchangeable product adds further costs to the development programme of a biosimilar. However, this investment is likely to provide return as it opens the door for automatic substitution and bypasses physician and patient resistance to switching. The first biosimilars approved as interchangeable are expected in the USA market in late 2018 or early 2019.

The EMA has been at the frontline of biosimilar regulation, issuing the first overarching guideline in 2005 and many other product-specific recommendations since then. However, interchangeability is not covered in the EMA guidelines and the decisions on interchanging and substituting are left to individual member states, which have access to the scientific evaluations performed by EMA's committees.[18] As a consequence, the European reality on this matter is somewhat heterogeneous. Scandinavian countries, such as Norway and Denmark, featured among the first to adopt an administrative-driven, large-scale switch from reference infliximab and etanercept to their corresponding biosimilars. National regulatory agencies from other countries, including France, England, the Netherlands, and Portugal, have recommended the adoption of switching policies and the transition to infliximab and etanercept biosimilars is starting to occur.[19-21]

In Europe, biosimilar acceptance has grown among patients and physicians despite the lack of structured educational programmes in most of these countries. Nonetheless, national rheumatology societies and patient associations have expressed their concerns on non-medical switching and interchangeability. Table 1 presents the position statements of rheumatology societies from European countries.[22-29] In summary, automatic substitution is consensually rejected because physicians consider it a risk to traceability and pharmacovigilance. Some societies are starting to accept non-medical switching if the physician remains at the centre of the switching process and certain conditions are met. Interchangeability is currently not recommended by most due to the limited evidence on multiple switching.

CURRENT EVIDENCE ON BIOSIMILAR SWITCHING

Not surprisingly, the greatest amount of data on biosimilar switching in the context of inflammatory rheumatic conditions comes from CT-P13 (Remsima®, Celltrion, Incheon, South Korea; Inflectra®, Hospira, Lake Forest, Illinois, USA), the biosimilar of infliximab, which was the first monoclonal antibody approved, almost 5 years ago. Nevertheless, it is important to note that these data comprise almost exclusively open-label extensions of randomised double-blind trials[30,31] and registry or single-centre observational studies, they assess only one transition from reference drug

to biosimilar, and many lack appropriate control arms. One exception is the NOR-SWITCH trial,[32] a double-blind Phase IV trial in which 482 patients (inflammatory bowel disease, axial spondyloarthritis [axSpA], rheumatoid arthritis [RA], psoriatic arthritis [PsA], and plaque psoriasis) from Norway on stable treatment with reference infliximab were randomised to continue on reference infliximab or switch to CT-P13. Disease worsening (primary endpoint) and safety at 52 weeks were not different between study arms in the overall population (95% confidence interval of group difference: -12.7–3.9%; 15% non-inferiority margin for disease worsening in the entire population), though this study was not powered to detect differences in individual disease groups.[32] A nationwide, prospective, observational study from the DANBIO registry assessed switching from reference infliximab to CT-P13 in 802 patients with RA, axSpA, and PsA, which found no difference in disease activity 3 months before and after switching in each disease subset.[33] One-year adjusted absolute retention rates but not crude retention rates were slightly lower compared to historical infliximab cohorts (83.4% versus 86.8%, p=0.03), which was attributed by the authors to probable nocebo effect and residual confounding.[33] In line with the latter finding, Tweehuysen et al.[34] concluded that subjective features were the main driver for discontinuation after 6 months of transition to CT-P13 in RA, axSpA, and PsA patients, also due to the probable nocebo-effect and incorrect causal attribution effects.[34] Many other studies assessed open-label single transitions to CT-P13 in individual centres with a variable number of patients, but with overall positive results. Although inflammatory bowel disease is out of the scope of this article, it is noteworthy that a growing body of evidence supports that efficacy, safety, and immunogenicity remain unchanged after switching to CT-P13, including in the paediatric setting.[35,36] Infliximab biosimilar SB2 (Flixabi®, Biogen, Cambridge, Massachusetts, USA) demonstrated comparable efficacy, safety, and immunogenicity to the reference drug in the extension of the Phase III trial in which RA patients receiving SB2 continued to receive SB2 and those receiving reference infliximab were re-randomised to either switch to SB2 or to continue on reference infliximab, from Week 54 to Week 78. This transition study maintained double-blind status and allowed for simultaneous comparison of the switched group with the ongoing reference and biosimilar groups.[37]

Evidence on switching to etanercept biosimilars is growing. The Phase III trial of etanercept biosimilar GP2015 (Erelzi®, Sandoz) was performed in a non-rheumatic population but is worth mentioning for its unique design of multiple-switching.[38] Following the initial 12-week parallel-group period, patients with moderate-to-severe chronic plaque-type psoriasis either remained on the original allocated drug or interchanged treatment drug three times over 6-week intervals. After 52 weeks, the multiple-switch arms showed no efficacy, safety, or immunogenicity differences as compared to the maintenance arms.[38] Full-text manuscripts assessing the switch to SB4 (Benepali®, Biogen, USA) include a Phase I single-blind PK study in healthy individuals and an open-label extension of the Phase III trial evaluating transition to SB4 up to Week 100 in RA patients, and neither reported any discrepancies in efficacy or safety outcomes after switch.[39,40] Data from 1,623 RA, axSpA, and PsA patients from the DANBIO registry were presented as an abstract and revealed no significant change in disease activity 3 months after the switch to SB4; 9% (129) stopped treatment after 5 months follow-up largely due to lack of effect and adverse events.[41] One-year results of this observational study were later presented as another abstract showing 18% (276 of 1,623 patients) treatment withdrawal but no update on efficacy outcomes was made.[42] The BIO-SPAN study[43] evaluated non-mandatory transitioning to SB4 in 635 RA, AxSpA, and PsA patients using a specific communication strategy to counter nocebo and attribution. Compared to baseline, there was no difference at 6 months in efficacy but persistence and decreases in DAS28-CRP and CRP were slightly lower for SB4 compared to an historical 2014 etanercept cohort.[43]

Adalimumab biosimilars have recently been approved and are expected to enter the European market in late 2018. Thus, evidence on switching is still scarce and is published mostly as abstracts. One exception is SB5 (Imraldi®, Biogen), for which there was a published double-blind Phase III trial demonstrating similar efficacy, safety, immunogenicity, and radiographic outcomes at 52 weeks in RA patients who

switched from reference adalimumab to SB5 at Week 24 compared to maintenance arms.[44] The BI 695501 (Cyltezo®, Boehringer Ingelheim, Germany) Phase III extension trial showed that a single transition had no impact on efficacy, safety, and immunogenicity in RA patients at 58 weeks when compared to those continuing on reference drug or BI 695501.[45] Adalimumab biosimilar ABP 501 (Amgevita®, Solymbic®, Amgem, USA) has interim results from one open-label single-arm extension study in which the transition from the reference drug at Week 26 was associated with sustained efficacy and safety in RA patients at Week 72.[46]

Evidence on switching to rituximab biosimilars GP2013 (Riximyo® and Rixathon®, Sandoz, Germany) and CT-P10 (Truxima®, Blitzima®, Ritemvia®, Rituzena®, Celltrion, South Korea) in rheumatic conditions is still restricted to small-sized studies with limited reporting of efficacy and safety outcomes.[47-49]

It is noteworthy that evidence on switching these and other biosimilars is expected to grow in the near future because there are several ongoing studies in rheumatic and non-rheumatic inflammatory conditions.

SWITCHING AND IMMUNOGENICITY

Apprehensions have been raised that switching patients from reference antibodies to biosimilars may lead to increased immunogenicity and consequent safety or efficacy problems. Switches occur when patients receive biosimilars but may also occur after manufacturing process changes lead to structural modifications or changes in the impurity profile of the biologic drug.[11,50] This situation occurred with multiple medicines such as darbepoetin or infliximab.[51,52] A commonly expressed concern is whether there is an increase in immunogenicity related to the act of switching itself. ADA assays offer the most sensitive method to detect immunogenicity; neutralising antibodies (NAB) assays are the most direct method to signal the potential clinical relevance of ADA. PK, efficacy, and safety events may be additional measures to detect clinically relevant immunogenicity.[4]

The authors searched immunogenicity data from confirmatory trials of approved biosimilars in rheumatic diseases. Data collected included the proportion of patients positive for ADA among all patients and the proportion of patients with NAB among ADA-positive patients. The authors identified 10 biosimilars approved by the EMA or FDA: three for adalimumab (BI 695501, SB5, and ABP 501) and infliximab (SB2, CT-P13, and infliximab-qbtx), and two for etanercept (GP2015 and SB4) and rituximab (CT-P10 and GP2013). Published data in EMA Public Assessment Reports (EPAR), FDA Clinical Summaries, PubMed, and European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) abstracts show that the duration of treatment in the 16 identified trials (which varied in design and methodology of ADA and NAB detection) ranged from 12 to 102 weeks.[38,53-57] The lowest proportions of ADA-positive (0–13%) and NAB-positive (0–3%) patients were observed in the trials of etanercept and its biosimilars, and the highest in the trials of infliximab and its biosimilars (ADA: 20–62%; NAB: 88–100%).[38,53-57] The proportions of ADA and NAB-positive patients in individual trials were similar between the originator and biosimilar products. Of note, in a 52-week trial of etanercept biosimilar SB4, the incidence of ADA by Week 52 was significantly lower in the SB4 arm (1% [3/299] versus 13% [39/296]; $p<0.001$).[53] This difference may have been due to an ADA assay bias in samples collected at Weeks 4 and 8. However, it was recently confirmed that SB4 has equivalent efficacy to reference etanercept but is associated with fewer injection site reactions and less immunogenicity. Clinical features were generally comparable between the treatment groups regardless of ADA status.[58] Cross-reactivity between ADA of biosimilar and reference drugs suggests that epitopes influencing the immune response are common to both drugs.[59-61]

The results from immunogenic response to biosimilars in naïve patients are reflected in nearly all published studies evaluating switching between a biologic and a biosimilar. A recent study examining data from published literature showed no differences in immunogenicity, safety, or efficacy. This assessment covered seven molecular entities and 14,225 individuals from multiple indications between 1993 and June 2017, but a subset analysis of anti-TNF and anti-CD20 biosimilars demonstrates equivalent results.[62] While there are limitations to some of

the individual studies, the cumulative results of these published data do not show significant differences in ADA or NAB after switching compared to subjects who were not switched. There was also no reported increase in treatment-related safety events, including loss of efficacy. Only two studies report loss of efficacy or high dropout rates after switching from reference medicine to biosimilar infliximab; the results of Kang et al.[63] and Yazici et al.[64] studies were not replicated in other studies of switching from reference to biosimilar infliximab. Although most studies evaluate the effects of a single switch, the authors argue that long-term experience with biologics (including interchanging between biologicals and between pre and post-modification batches of the same drug) gives a strong indication that multiple switches would not create problems for patients. However, further studies are warranted to confirm this hypothesis.

CONCLUSION

Current knowledge is favourable to switching from reference drugs to biosimilars in the treatment of inflammatory rheumatic conditions. However, one must consider that evidence comes essentially from a few observational studies and double-blind or open-label extensions of Phase III trials, performed on a reduced number of patients with limited duration of follow-up, mostly on CT-P13 and SB4. This evidence cannot be extrapolated to other biosimilars and it is arguable whether it should be extrapolated to other conditions for which the biosimilar is approved. There will always be a knowledge gap because studies do not cover all the switching possibilities taking place in real life. It is highly unlikely that manufacturers hold trials assessing switch between different biosimilars because this would represent additional costs and still provide insufficient answers.

It is the authors' strong belief that a robust state-of-the-art demonstration of biosimilarity combined with rigorous post-marketing pharmacovigilance mechanisms involving pharmacists, prescribers, and patients will bring reassurance to switching and interchangeability. Prescribers and pharmacists should ensure adequate registration of biosimilar trade name and batch number. Physicians should be encouraged to spontaneously report adverse events and use national registries to document efficacy, safety, and immunogenicity after switching. Patients should be fully knowledgeable about the biopharmaceutical they were prescribed and properly educated on how to report possible adverse events.

It is also the authors' belief that the prescribing physician should be in the centre of the switching decision. This decision should be made on a case-by-case basis taking into consideration patient and disease characteristics, as well as drug and device-related factors. National or regional authorities may compel hospital pharmacies to automatically substitute a reference biologic for a biosimilar as a means to rapidly achieve cost containment. For the time being, we consider this administrative substitution unacceptable because it compromises the chain of pharmacovigilance, and ultimately endangers not only the safety of patients but also the future of biosimilars in the treatment of rheumatic conditions.

References

1. Putrik P et al. Inequities in access to biologic and synthetic DMARDs across 46 European countries. Ann Rheum Dis. 2014;73(1):198-206.
2. European Medicines Agency. Remsima - Assessment Report. 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002576/WC500151486.pdf. Last accessed: 8 June 2018.
3. QuintilesIMS. The impact of biosimilar competition in Europe. 2017. Available at: http://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017_V9.pdf. Last accessed: 8 June 2018.
4. Gonçalves J et al. Biosimilar monoclonal antibodies: Preclinical and clinical development aspects. Clin Exp Rheumatol. 2016;34:698-705.
5. European Medicines Agency. Guideline on similar biological medicinal products containing monoclonal antibodies – Non-clinical and clinical issues. 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf. Last accessed: 8 June 2018.
6. Araújo F et al. Biosimilar DMARDs: What does the future hold? Drugs. 2016;76:629-37.
7. European Medicines Agency. European Public Assessment Reports. 2018. Available at: http://www.ema.europa.eu/ema/index.jsp?status=Authorised&alreadyLoaded=true&searchTab=searchByAu-

thType&searchType=name&curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&searchGenericType=biosimilars&keyword=Enter+keywords&mid=WC0b01ac058001d124&pageNo=2. Last accessed: 8 June 2018.

8. Rashid N et al. Switching to Omnitrope® from other recombinant human growth hormone therapies: A retrospective study in an integrated healthcare system. Biol Ther. 2014;4(1-2):27-39.
9. López-Siguero J et al. Ten years' clinical experience with biosimilar human growth hormone: A review of efficacy data. Drug Des Devel Ther. 2017;11:1489-95.
10. Mikhail A, Farouk M. Epoetin biosimilars in Europe: Five years on. Adv Ther. 2013;30(1):28-40.
11. Ebbers HC et al. The safety of switching between therapeutic proteins. Expert Opin Biol Ther. 2012;12(11):1473-85.
12. Beck M et al. Rheumatologists' perceptions of biosimilar medicines prescription: Findings from a French web-based survey. BioDrugs. 2016;30(6):585-92.
13. Waller J et al. Assessing physician and patient acceptance of infliximab biosimilars in rheumatoid arthritis, ankylosing spondyloarthritis and psoriatic arthritis across Germany. Patient Prefer Adherence. 2017;11:519-30.
14. Jacobs I et al. Patient attitudes and understanding about biosimilars: An international cross-sectional survey. Patient Prefer Adherence. 2016;10:937-48.
15. Perez IA et al. Ensuring the consistency of biosimilars. Curr Pharm Des. 2017;23(44):6733-8.
16. The US Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product. 2017. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf. Last accessed: 8 June 2018.
17. The United States Senate. Title VII—improving access to innovative medical therapies. subtitle a—biologics price competition and innovation. 2009. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ucm216146.pdf. Last accessed: 8 June 2018.
18. European Medicines Agency. Biosimilars in the EU - Information guide for healthcare professionals. 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf. Last accessed: 8 June 2018.
19. NHS England. Biosimilar Medicines. 2017. Available at: https://www.england.nhs.uk/medicines/biosimilar-medicines/. Last accessed: 8 June 2018.
20. GaBI. The evolution of switching and substitution of biosimilars in Europe. 2017. Available at: http://gabionline.net/Reports/The-evolution-of-switching-and-substitution-of-biosimilars-in-Europe. Last accessed: 8 June 2018.
21. Comissão Nacional Farmácia e Terapêutica. Utilização de medicamentos biossimilares e mudança de medicamento biológico de referência para um biossimilar. 2018. Available at: http://www.infarmed.pt/documents/15786/1816213/Orientação+n+º+5+-+Utilização+de+medicamentos+biossimilares/ddf4797c-a329-40d7-8d92-a1635a2f2ea7. Last accessed: 8 June 2018.
22. British Society for Rheumatology. British Society for Rheumatology position statement on biosimilar medicines (Revised January 2017). 2017. Available at: https://www.nras.org.uk/data/files/revised_bsr_biosimilars_position_statement_jan_2017.pdf. Last accessed: 8 June 2018.
23. Atzeni F et al. Position paper of Italian rheumatologists on the use of biosimilar drugs. Clin Exp Rheumatol. 2015;33(1):1-4.
24. Deutsche Rheuma-Liga. Positionierung der Deutschen Rheuma-Liga Bundesverband e.V. zur Einführung von Biosimilars in Deutschland. 2014. Available at: https://www.rheuma-liga.de/biosimilars/. Last accessed: 8 June 2018.
25. Sociedad Española de Reumatología. Documento de posicionamiento de la Sociedad Española de Reumatología sobre fármacos biosimilares. 2018. Available at: https://www.ser.es/wp-content/uploads/2015/09/Posicionamiento-Biosimilares.pdf. Last accessed: 8 June 2018.
26. Araújo F et al. The Portuguese Society of Rheumatology position paper on the use of biosimilars - 2017 update. Acta Reumatol Port. 2017;42(3):219-28.
27. Schaeverbeke T et al. Biosimilars: An opportunity. Position statement of the French Rheumatology Society (SFR) and Inflammatory Rheumatic Disease Club (CRI). Joint Bone Spine. 2018. [Epub ahead of print]
28. Royal Belgian Society for Rheumatology. Biosimilars in rheumatic diseases. Position of the Royal Belgian Society of Rheumatology. 2015. Available at: https://www.reumanet.be/sites/default/files/Biosimilars%20KBVRSRBR%20viewpoint.pdf. Last accessed: 8 June 2018.
29. The Finnish Society for Rheumatology. The use of biosimilars in rheumatological therapeutical indications - Statement of The Finnish Society for Rheumatology. 2015. Available at: http://www.reumatologinenyhdistys.fi/files/Finnish-Society-for-Rheumatology-Statement-on-biologic-English2015.pdf. Last accessed: 8 June 2018.
30. Yoo DH et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: Comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis. 2017;76(2):355-63.
31. Park W et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Ann Rheum Dis. 2017;76(2):346-54.
32. Jørgensen K et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): A 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017;389(10086):2304-16.
33. Glintborg B et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. Ann Rheum Dis. 2017;76(8):1426-31.
34. Tweehuysen L et al. Subjective complaints as the main reason for biosimilar discontinuation after open-label transition from reference infliximab to biosimilar infliximab. Arthritis Rheumatol. 2018;70(1):60-8.
35. Gisbert JP, Chaparro M. Switching from an originator anti-TNF to a biosimilar in patients with inflammatory bowel disease: Can it be recommended? A systematic review. Gastroenterol Hepatol. 2018. [Epub ahead of print]
36. Komaki Y et al. Systematic review with meta-analysis: The efficacy and safety of CT-P13, a biosimilar of anti-tumour necrosis factor-α agent (infliximab), in inflammatory bowel diseases. Aliment Pharmacol Ther. 2017;45(8):1043-57.
37. Smolen J et al. Safety, immunogenicity and efficacy after switching from reference infliximab to biosimilar SB2 compared with continuing reference infliximab and SB2 in patients with rheumatoid arthritis: Results of a randomised, double-blind, Phase III transition study. Ann Rheum Dis. 2018;77(2):234-40.
38. Griffiths CEM et al. The EGALITY study: A confirmatory, randomised, double-blind study comparing the

efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, versus the originator product in patients with moderate to severe chronic plaque-type psoriasis. Br J Dermatol. 2017;176(4):928-38.

39. Lee Y et al. A randomised Phase I pharmacokinetic study comparing SB4 and etanercept reference product (Enbrel®) in healthy subjects. Br J Clin Pharmacol. 2016;82(1):64-73.
40. Emery P et al. Long-term efficacy and safety in patients with rheumatoid arthritis continuing on SB4 or switching from reference etanercept to SB4. Ann Rheum Dis. 2017. [Epub ahead of print].
41. Glintborg B et al. Clinical outcomes from a nationwide non-medical switch from originator to biosimilar etanercept in patients with inflammatory arthritis after 5 months follow-up. Results from the DANBIO registry. Ann Rheum Dis. 2017;76(Suppl 2):553.
42. Glintborg B et al. One-year clinical outcomes in 1623 patients with inflammatory arthritis who switched from originator to biosimilar etanercept - An observational study from the Danish Danbio Registry. Arthritis Rheumatol. 2017;69(suppl 10).
43. Tweehuysen L et al. Open-label non-mandatory transitioning from originator etanercept to biosimilar SB4: 6-month results from a controlled cohort study. Arthritis Rheumatol. 2018. [Epub ahead of print]
44. Weinblatt M et al. Switching from reference adalimumab to SB5 (adalimumab biosimilar) in patients with rheumatoid arthritis: 52-week Phase 3 randomized study results. Arthritis Rheumatol. 2018;70(6):832-40.
45. Cohen SB et al. Similar efficacy, safety and immunogenicity of adalimumab biosimilar BI 695501 and Humira reference product in patients with moderately to severely active rheumatoid arthritis: Results from the Phase III randomised VOLTAIRE-RA equivalence study. Ann Rheum Dis. 2018;77(6):914-21.
46. Cohen SB et al. ABP 501 long-term safety/efficacy: Interim results from an open-label extension study. Arthritis Rheumatol. 2016;68(suppl 10).
47. Park W et al. Efficacy and safety of switching from innovator rituximab to biosimilar CT-P10 compared with continued treatment with CT-P10: Results of a 56-week open-label study in patients with rheumatoid arthritis. BioDrugs. 2017;31(4):369-77.
48. Shim SC et al. Efficacy and safety of rituximab biosimilar, CT-P10, after a single switch from innovator rituximabs in patients with rheumatoid arthritis: Results from Phase 3 randomized controlled trial over 72 weeks. Arthritis Rheumatol. 2017;69(suppl 10).
49. Tony HP et al. Comparison of switching from the originator rituximab to the biosimilar rituximab GP2013 or re-treatment with the originator rituximab in patients with active rheumatoid arthritis: Safety and immunogenicity results from a multicenter, randomized, double-blind study. Arthritis Rheumatol. 2017;69(Suppl 10).
50. Chingcuanco F et al. Bioequivalence of biosimilar tumor necrosis factor-alpha inhibitors compared with their reference biologics: A systematic review. Ann Intern Med. 2016;165(8):565-74.
51. European Medicines Agency. Assessment Report for Aranesp. 2008. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000332/WC500026148.pdf. Last accessed: 11 July 2018.
52. Endrenyi L et al. "Biosimilar Drug Product Development," 2017. Volume 216. Boca Raton: CRC Press.
53. Emery P et al. A Phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2017;76(1):51-7.
54. Park W et al. A randomised, double blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis. 2013;72(10):1605-12.
55. Yoo D et al. Randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: The PLANETRA study. Ann Rheum Dis. 2013;72(10):1613-20.
56. Choe JY et al. A randomised, double-blind, Phase III study comparing SB2, an infliximab biosimilar to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2017;76(1):58-64.
57. Palaparthy R et al. A randomized study comparing the pharmacokinetics of the potential biosimilar PF-06438179/GP1111 with Remicade® (infliximab) in healthy subjects (REFLECTIONS B537-01). Expert Rev Clin Immunol. 2018;14(4):329-36.
58. Girolomoni G et al. Comparison of injection-site reactions between the etanercept biosimilar SB4 and the reference etanercept in patients with rheumatoid arthritis from a Phase III study. Br J Dermatol. 2018;178(3):e215-6.
59. Reinisch W et al. Evaluation of the cross-reactivity of antidrug antibodies to CT-P13 and infliximab reference product (remicade): An analysis using immunoassays tagged with both agents. BioDrugs. 2017;31(3):223-37.
60. Ruiz-Argüello MB et al. Antibodies to infliximab in Remicade-treated rheumatic patients show identical reactivity towards biosimilars. Ann Rheum Dis. 2016;75(9):1693-6.
61. Ben-Horin S et al. Cross-immunogenicity: Antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. Gut. 2016;65(7):1132-8.
62. Cohen HP et al. Switching reference medicines to biosimilars: A systematic literature review of clinical outcomes. Drugs. 2018;78(4):463-78.
63. Kang YS et al. Clinical experience of the use of CT-P13, a biosimilar to infliximab in patients with inflammatory bowel disease: A case series. Dig Dis Sci. 2015;60(4):951-6.
64. Yazici Y et al. A descriptive analysis of real-world treatment patterns in a Turkish rheumatology population that continued innovator infliximab (Remicade) therapy or switched to biosimilar infliximab. Arthritis Rheumatol. 2016;68(Supp 10).

Primary Sjögren's Syndrome in the Elderly: Does Age of Onset Make a Difference?

Authors: *Ciro Manzo,[1] Maria Maslinska[2]

1. Internal and Geriatric Medicine Department, Rheumatologic Outpatient Clinic Hospital "Mariano Lauro", Naples, Italy
2. National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, Poland

*Correspondence to cirmanzo@libero.it

Disclosure: The authors have declared no conflicts of interest.

Received: 20.02.18

Accepted: 18.05.18

Keywords: Classification criteria, diagnostic criteria, differential diagnosis, elderly, elderly-onset primary Sjögren's syndrome (EOpSS), primary Sjögren's syndrome (pSS), sicca syndrome.

Citation: EMJ Rheumatol. 2018;5[1]:75-82.

Abstract

Primary Sjögren's syndrome (pSS) is a relatively common disease and one of the most common rheumatic diseases of autoimmune and inflammatory origin. It is primarily associated with symptoms of dryness, mainly in the mouth and eyes, but it can also manifest in the internal organs. Epidemiological studies have highlighted that elderly-onset pSS (EOpSS) is common, and it is known that sicca syndrome is a feature often observed in the elderly and can be induced by several factors. However, the presence of autoantibodies in older patients with sicca syndrome can be age-related and does not mean pSS is present. This review article presents the most important elements for making a correct diagnosis of EOpSS and considers clinical and/or laboratory differences between older and younger pSS patients. According to data from the literature, EOpSS is not a distinct subset of disease when compared with younger-onset pSS.

INTRODUCTION

Primary Sjögren's syndrome (pSS) is an autoimmune disease that typically has exocrine gland involvement and can lead to sicca syndrome, although internal organs may also be affected. Due to the ever-growing access to rheumatological diagnostic assessments, including immunological (presence of autoantibodies) and histopathological (salivary gland biopsy), early diagnosis is possible. In the elderly, sicca syndrome is a common feature that can be induced by several factors. In addition, the presence of autoantibodies in older patients with sicca syndrome can be age-related and does not mean pSS is present. Knowledge of all clinical elements is very important for a correct diagnosis of elderly-onset pSS (EOpSS). The aim of this review article is to provide information to facilitate an understanding of how to correctly diagnose EOpSS; furthermore, the clinical and/or laboratory differences between EOpSS and younger-onset pSS are also highlighted.

PRIMARY SJÖGREN'S SYNDROME PATHOGENESIS

The pathogenesis of pSS is characterised by epithelial damage, release of autoantigens, and activation of innate and acquired immunity;

however, B lymphocytes and the production of autoantibodies play the main role in pSS pathogenesis.[1,2] The factors that trigger the pathophysiological phenomena in pSS include genetic predisposition (for genes encoding human leukocyte antigen [HLA]-B8, HLA-Dw3, HLA-DR3, and HLA-DRw52), infection (especially Epstein–Barr virus),[3] environmental factors, such as ultraviolet radiation,[4] and hormonal disorders.[5,6] Smoking has also been associated with pSS development; however, recent observations have been made about the lack of influence, and even positive effect, of smoking on the course of pSS.[7,8] Among antibodies against extractable nuclear antigens, those against small ribonucleoproteins SS-A (Ro) and SS-B (La) are particularly important in pSS diagnosis and pathogenesis.[9]

EPIDEMIOLOGY OF PRIMARY SJÖGREN'S SYNDROME

Epidemiological data show that pSS is a relatively common disease and one of the most common rheumatic diseases of autoimmune and inflammatory origin; however, the incidence and prevalence may vary depending on the diagnostic criteria used.[10] The prevalence of pSS, based on various sources, ranges from 0.72–2.70% of the general population, but some studies have reported prevalence rates as high as 5.00%.[11] Many studies have confirmed that pSS is more common in women (female: male ratio of 9:1) and mainly affects individuals between the ages of 40 and 60 years, with the disease most frequently occurring in people around 50 years of age.[10-12]

EPIDEMIOLOGICAL DATA FOR ELDERLY-ONSET PRIMARY SJÖGREN'S SYNDROME

EOpSS has an estimated overall prevalence of approximately 3% but epidemiological data are very heterogeneous and prevalence depends on variables such as geographic area and, above all, diagnostic criteria. Relatively old data presented in a study by Drosos et al.,[13] in which 62 healthy volunteers with a mean age of 81 years (range: 67–95 years) were examined, confirmed pSS in 4.83% of the study group. The authors suggested that pSS in elderly people is subclinical, benign, and relatively common.[13] In another study conducted in 2008,[14] researchers showed that in an elderly group (aged 71–74 years) pSS was confirmed in 3.39% (95% confidence interval [CI]: 2.77–4.14) according to the European classification criteria from 1993, and in 1.40% (95% CI: 1.02–1.92) according to the revised European classification criteria from 1996. The prevalence of pSS in the younger group (aged 40–44 years) was lower, totalling 0.44% (95% CI: 0.34–0.57) and 0.22% (95% CI: 0.15–0.32), respectively.[14] In an Italian cohort,[15] 6% of patients had EOpSS, while in a Tunisian cohort this value was higher at 30%.[16] Johansson et al.[17] highlighted that symptoms of dryness were reported in >30% of elderly people, with the percentage increasing with age, and that symptoms were more frequently expressed in women. In the Lin et al.[18] population-based study, dry eye symptoms had higher prevalence in elderly Asian populations than in Caucasian populations, with as much as 47.5% of the Asian group diagnosed with dry eye and in need of topical treatment.

CLINICAL FEATURES OF PRIMARY SJÖGREN'S SYNDROME

Destruction of the lacrimal or salivary glands is the cause of the most common complaint associated with pSS; however, such dryness can also affect the mucous membranes of the bronchial tree, gastrointestinal tract, and vagina, with the most commonly occurring symptoms being bronchitis and coughing. Some more general symptoms have been reported by pSS patients, and some of the particularly frequent symptoms include fatigue, general weakness, and chronic pain; these may also be a cause of diagnostic confusion, especially in older patients.

The common organ lesions observed in pSS are presented in Table 1. Of all the phenomena listed, changes in the lungs deserve particular attention because of their frequency; for example, interstitial lung disease occurs in approximately 10–20% of pSS cases.[19] Most often this is a nonspecific interstitial pneumonia, but these changes may remain unrecognised for a long time since the classic radiological examination is insufficient to establish a diagnosis at an earlier stage.[20] In older patients, the higher likelihood of infection and drug resistance can represent specific critical issues.

Table 1: Organ and system-specific symptoms of primary Sjögren's syndrome.

Organ or system	Symptoms
Eye	DES, keratoconjunctivitis sicca, corneal erosions, filamentary keratitis, corneal ulcers, decreased vision, eye infections, and cicatrising conjunctivitis.
Salivary glands	Mouth dryness, burning of the tongue, increased dental caries, trouble swallowing, difficulty speaking, and enlarged parotid glands (periodontitis).
Joints	Arthralgia and arthritis.
Skin	Annular erythema, palpable purpura (vasculitis, and cryoglobulinaemia), and xerosis (primary Sjögren's syndrome, and hypothyreosis).
Haematologic	Leucopenia, neutropenia, thrombocytopenia, anaemia, cryoglobulinaemia, monoclonal proteins, MGUS, and mucosa-associated lymphoid tissue lymphoma.
Muscle	Myalgia and myositis.
Ears, nose, and throat	Otitis media, nosebleeds, crusting damage, poor sense of smell, impeded swallowing, and hearing loss.
Bronchi	Recurrent bronchitis, bronchioles, bronchial hyper-reactivity, and dry cough.
Lung	Interstitial lung disease (NSIP, LIP, UIP, and OP), pleurisy, and pleural effusion.
Peripheral nervous system	Sensory and combined sensory-motor neuropathy, mononeuropathy with cranial nerve involvement, mononeuropathy, multiple mononeuropathy (mononeuritis multiplex) and demyelinating syndromes, including Smith-Magenis-like syndrome and autonomic neuropathies, and restless leg syndrome.
Central nervous system	Focal lesions, changes with pyramidal symptoms, encephalopathy, changes typical for aseptic meningitis, transverse myelitis, optic neuropathy, and demyelinating symptoms (Smith–Magenis-like syndrome).
Kidney	Interstitial nephritis with distal renal tubular acidosis, glomerulonephritis with coexisting cryoglobulinaemia, and urolithiasis.
Gastrointestinal tract	Gastro-oesophageal reflux, gastritis, primary biliary cirrhosis,* autoimmune hepatitis,* and cholelithiasis.
Cardiovascular system	Vasculitis (leukocytoclastic vasculitis), purpura, livedo reticularis, Raynaud's phenomenon, pericarditis, carditis, pleuritis, and pulmonary arterial hypertension.
Other	Autoimmune thyroiditis*

*Autoimmune diseases commonly accompanying primary Sjögren's syndrome.

DES: dry eye syndrome; LIP: lymphocytic interstitial pneumonia; MGUS: monoclonal gammopathy of undetermined significance; NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia; UIP: usual interstitial pneumonia.

CLASSIFICATION AND DIAGNOSTIC CRITERIA

Criteria for the diagnosis of pSS have evolved over the years since the discovery of the disease, along with the broadening of immunological knowledge and the improvement of assessment techniques for the symptoms of dryness. All principal cohorts in the literature are based on the classification criteria of the 1993 European Community Study Group (ECSG)[21] and the 2002 American European Consensus Group (AECG) criteria.[22] The AECG criteria built upon previous preliminary criteria proposed in 1993 by a European collaborative group. It considered six items, two of which were subjective (ocular and oral symptom complaints by the patients) and four based on objective findings. These objective findings are Schirmer's test, Rose Bengal score according to the van Bijsterveld score, minor salivary biopsy with a focus score (FS) >1, and objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests: unstimulated whole salivary flow <1.5 mL in 15 minutes; parotid sialography showing the presence of diffuse sialectasis (punctate, cavitary, or destructive pattern), without evidence of obstruction in the major ducts; salivary scintigraphy showing delayed uptake,

reduced concentration, and/or delayed excretion of trace; and presence in the serum of antibodies to Ro (SSA) or La (SSB) antigens, or both. In patients without any potentially associated disease, pSS may be defined as the presence of four of the aforementioned six items (histopathology and autoantibodies are mandatory) or presence of three of the four objective criteria.

At the end of 2016, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) presented jointly established pSS diagnostic criteria.[23] Of all the laboratory tests, diagnostic importance was attributed only to SSA/Ro autoantibodies (3 points). Ocular staining score and Schirmer's test were retained as part of the ophthalmologic examination (1 point), while the measurement of unstimulated salivary flow was proposed for the assessment of salivary gland function (1 point). Histopathological examination of minor salivary gland biopsies with the assessment of the FS of the infiltrate cells remained an important element of diagnosis (FS >1 gives 3 points). The diagnosis is made if a patient presents with a sum of ≥4 points, but a cut-off of 5 points instead of 4 raises the specificity of the criteria from 89% to 98%.[24]

For the diagnosis of pSS, it is important to assess the established exclusion criteria, such as head and neck radiation treatment, active hepatitis C virus (HCV) infection (confirmed using PCR), AIDS, sarcoidosis, amyloidosis, graft versus host disease, and immunoglobulin G4-related disease. Additionally, in the evaluation of dry eye symptoms, patients using eye drops for glaucoma daily and those who have had corneal surgery or cosmetic eyelid surgery in the last 5 years are scored 0 points.

Furthermore, it should be considered that some drugs, even when not applied locally in the form of eye drops but administered in other ways, reduce the secretion of tears or saliva.[25] These drugs include anticholinergics, antidepressants (tricyclic or selective serotonin reuptake inhibitors), antihypertensives (terazosin, prazosin, clonidine, and atenolol, antihistamines, antireflux drugs, diuretics, and benzodiazepines.

Biopsy of minor salivary glands remains a gold standard for proving inflammation and infiltration of the salivary glands by mononuclear cells. This assessment should be performed by a pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis and FS count.[24] FS means no less than 50 mononuclear cells per 4 mm^2 of the glandular section.

SYMPTOMS AND DIAGNOSTIC CRITERIA IN OLDER PATIENTS

The relationship between disease, drugs, radiotherapy (RT), age-related glandular functions, and sicca syndrome is widely described in the literature. In the case of EOpSS, these factors should be taken into account to avoid misdiagnosis. For lachrymal and salivary glands, for example, older age is associated with a reduction of tear and/or saliva production. Since the likelihood of a positive Schirmer's test result gradually increases with advancing age,[26] the test in an elderly individual cannot be used in isolation to diagnose EOpSS. Furthermore, in clinical practice, older persons have comorbidities and are often prescribed numerous drugs that can induce salivary and/or lachrymal gland dysfunction or alter laboratory test results. Indeed, it is understandable that drugs with antagonistic actions on autonomic receptors and that are used to treat dysfunction in the various effectors of the autonomic nervous system may also affect the functions of salivary glands and thus cause oral dryness. Some patients taking enalapril and lisinopril present with xerostomia,[25,27] which can also be induced by nonsteroidal anti-inflammatory drugs, such as ibuprofen, naproxen, and piroxicam.[27] Xerostomia is also frequent in patients with head and neck cancer being treated with RT. Usually, radiation-induced xerostomia has an early onset; in the first week after therapy, half of patients present with a decrease in salivary flow and, after head and neck RT, salivary glands have a limited capacity for repair, especially with mean doses above 40 Gy.[28]

HCV infection represents another exclusion criterion. In 1992, Haddad et al.[29] reported lymphocytic sialadenitis in 57% of HCV-infected patients and 5% of controls. Clinical pathology and biologic similarities between these two diseases suggest common pathogenic pathways.[29]

Box 1: Differences in primary Sjögren's syndrome between a group of older and younger patients.

Younger patients with pSS	Elderly patients with pSS
› ANA in low titre › Anti-SSA and anti-SSB antibodies › Inflammation with salivary glands and oedema › Fewer or no signs of dryness	› Presence of ANA and RF (more frequently) › Anti-SSA and anti-SSB antibodies › Atrophic changes in the salivary glands with less inflammation › Dryness symptoms (eye, mouth, and vagina) related to age, pSS, drugs, or comorbidities (e.g., diabetes)
Symptoms other than dryness	
› Weakness › Numbness › Arthralgia › Rare arthritis › Autoimmune thyroiditis (Hashimoto's disease) › Pregnancy and neonatal disturbances due to the presence of anti-SSA antibodies	› More severe muscular weakness › Sarcopenia › Arthralgia › Arthritis › Osteoarthritis › Cardiovascular disease › COPD › Diabetes › Obesity › Autoimmune thyroiditis › Higher risk of malignancy: lymphomas and other cancers

ANA: antinuclear antibodies; COPD: chronic obstructive pulmonary disease; pSS: primary Sjögren's syndrome; RF: rheumatoid factor; SSA: serum of antibodies to Ro; SSB: serum of antibodies to La.

In clinical practice, the availability of new, very effective drugs for HCV eradication underlines the necessity to reconsider the diagnosis of pSS once the absence of serum HCV RNA has been obtained.

In older persons, a biopsy of the minor salivary glands can constitute an important diagnostic conundrum. In labial salivary gland (LSG) biopsies, a focal lymphocytic sialadenitis with >50 mononuclear cells in a periductal or perivascular localisation is considered the most specific finding for pSS diagnosis. A protocol published in 2011 by the Sjögren's International Clinical Collaborative Alliance (SICCA) underlined that these foci must occur adjacent to normal appearing acini.[30] In older patients, acinar atrophy and fibrosis can be age-related or due to expression of nonspecific chronic sialadenitis, which can introduce a confounding element (for example, availability of <4–6 glands suitable for diagnostic evaluation). More recently, the Sjögren's histopathology workshop by the EULAR Sjogren's Syndrome Experimental and Translational Investigative Alliance Study Group (ESSENTIAL) provided standardised consensus guidance for the use of LSG histopathology in the classification of pSS. The diagnostic importance of foci that are adjacent to normal parenchyma was emphasised. Furthermore, recommendation number 6 was that the extent of the atrophic features should be graded (as mild, moderate, and severe) in addition to the presence or absence of focal lymphocytic sialadenitis; this had a level C strength of recommendation. Another recommendation (number 10) concerning the necessity that all foci should be included in the FS and in foci calculations, even when adjacent to abnormal acinus or ducts, obtained a level D in guidance proposed for the clinical trials.[31]

AUTOANTIBODIES AND AUTOIMMUNE DISEASES IN THE ELDERLY: THE IMPORTANCE OF IMMUNOSENESCENCE

In elderly individuals, some aspects of the immune system function are lost. During an individual's lifetime, the immune system undergoes changes: the mechanisms of acquired immunity may, over time, outweigh the pool of naïve lymphocytes that have not yet come into contact with an antigen and, as such,

the number of antibodies and immunological complexes grows, as well as the number of memory cells due to the numerous pathogens encountered.[32] In the elderly, an increase in proinflammatory cytokines (age-associated low-grade inflammation) is also observed.[33] With age, the frequency of antinuclear antibodies (ANA) and other antibodies increases, but the incidence of autoimmune diseases is less frequent in individuals >75 years than in the 30–50 year age range. Among the systemic diseases of connective tissue, systemic lupus erythematosus occurs in elderly individuals less often than pSS.[34] The antibodies most frequently present in pSS are antibodies against the small ribonucleoproteins SSA/Ro and SSB/La. Researchers have shown that patients diagnosed before 45 years of age have higher anti-SSA and SSB autoantibody concentrations (62.5%) than patients with EOpSS (20.8%).[35,36] The presence of rheumatoid factor (RF) is often observed in healthy elderly people, possibly as a consequence of the age-related immune deregulation.[37] In the above cited papers,[35,36] RF concentrations in patients with pSS were higher in the group with earlier diagnosis before the age of 45 years.

PRIMARY SJÖGREN'S SYNDROME AND CANCER RISK

Patients with pSS are particularly vulnerable to the development of lymphomas, including non-Hodgkin's lymphoma from B lymphocytes, although less frequently from T and natural killer cells. Patients with pSS present 9–44-times more often with lymphomas than healthy populations.[38,39] Marginal zone B cell lymphoma is most often described, which includes mucosa-associated lymphoid tissue lymphoma. Less frequently, but with great clinical relevance, disseminated lymphoma from large B lymphocytes occurs (diffuse large B cell lymphoma).

ELDERLY-ONSET PRIMARY SJÖGREN'S SYNDROME AND CANCER RISK

Age itself is one of the most important elements for the development of malignancies. Despite this, data regarding the neoplastic status of EOpSS patients are very scarce and primarily highlighted by case reports.[40] One study evaluated the incidence and standardised incidence ratio of breast cancer in a cohort of elderly patients with some chronic autoimmune diseases and did not find an increased risk in the group of patients with EOpSS.[41]

DIFFERENCES BETWEEN YOUNGER AND OLDER PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME

As shown in Box 1, some differences can be underlined in EOpSS compared to younger pSS patients.

COHORT STUDIES PRESENT IN THE LITERATURE

In a search of PubMed, four studies were identified that reported on cohorts of patients with EOpSS, totalling 99 patients (Table 2). In these studies, disease onset was determined based on the occurrence of symptoms strongly suggestive of pSS; in three of the studies, elderly onset was set at age 65 years, but in the García-Carrasco et al.[42] study, it was set at 70 years. Each study used the diagnostic criteria commonly being used at the time of publication.

A high percentage of patients with ANA positivity presented in the Botsios et al.[15] cohort; this was only partially confirmed in the other three studies. Up to 20% of healthy people can have ANA positivity, and this probability is much higher in older people as a consequence of the generally accepted hypothesis that immunosenescence causes a decrease of self-regulatory mechanisms with increased autoantibody production. With the exception of the Chebbi et al.[16] data, the presence of anti-SSA and anti-SSB were similar in all studies. Given the absence of phenotypic features associated with isolated anti-SSB autoantibodies, and the low negative and positive likelihood ratios for the diagnosis of pSS, the recent classification of the ACR and EULAR[23] excluded anti-SSB-positivity from the diagnostic criteria. Differences between studies were found in clinical characteristics of patients, with neurological and pulmonary involvement more often observed in the Chebbi et al.[16] cohort and Raynaud's phenomenon more frequently observed in the Botsios et al.[15] cohort.

Table 2: Clinical manifestations, laboratory data, classification criteria, histological results, and cancer risk in four literature studies.

Study	Number of patients	Classification criteria	Xerostomia (%)	Xerophthalmia (%)	AI (%)	NI (%)	PI (%)	RI (%)	HM	RP (%)	Thyroiditis (%)	ANA (%)	Anti-SSA (%)	Anti-SSB (%)	RF	Positive LSG biopsy (%)	Cancer risk
Botsios et al.,[15] 2011	21	AECG, 2002	71.4	76.1	66.7	4.7	4.7	4.7	14.2	23.8	9.5	85.7	66.7	52.3	71.0	52.3	NR
Chebbi et al.,[16] 2015	18	AECG, 2002	100.0	100.0	88.8	66.6	44.4	11.1	5.5	5.5	NR	44.4	33.3	11.1	NR	NR	NR
Tishler et al.,[37] 2001	17	San Diego criteria	100.0	94.0	29.0	16.0	NR	NR	NR	12.0	NR	36.0	12.0	12.0	NR	NR	NR
García-Carrasco et al.,[42] 2002	43	ECSG, 1993	98.0	91.0	23.0	12.0	16.0	7.0	NR	7.0	14.0	65.0	23.0	16.0	29.0	76.0*	NR

*LSG biopsy was performed in 25 of the 43 patients.

AECG: American European Consensus Group; AI: articular involvement; ANA: antinuclear antibodies; ECSG: European Community Study Group; HM: haematological manifestations; LSG: labial salivary gland; NI: neurological involvement; NR: not recorded; PI: pulmonary involvement; RF: rheumatoid factor; RI: renal involvement; RP: Raynaud's phenomena; SSA: serum of antibodies to Ro; SSB: serum of antibodies to La.

No data regarding cancer risk were present in the four studies. LSG biopsies were performed in two cohorts.[15,42]

Lastly, when the authors compared older-group data with younger-group data, differences were only highlighted in the study by Chebbi et al.[16] In this study, pulmonary involvement was more frequent in the older group (although not statistically significant), whereas the difference in levels of ANA, anti-SSA, and anti-SSB was statistically significant in the younger group. In the other three studies, clinical and laboratory results of EOpSS patients were quite similar to those in younger patients. Demographic factors and differences in genetic predisposition have a potential role in explaining these differences. The reduced expression of immunological features in patients with EOpSS (more evident in the Chebbi et al.[16] cohort but present in all the cohorts considered) may reflect the senescence of the immune system.

CONCLUSION

According to the data found in the literature, it can be concluded that EOpSS is not a distinct subset of disease, unlike elderly-onset rheumatoid arthritis or elderly-onset systemic lupus erythematosus, for example. However, age-related manifestations, such as dryness symptoms, ANA, and RF positivity, as well as all the comorbidities and therapies that can induce sicca syndrome, should be carefully evaluated to avoid misdiagnosis.

Similarly, Schirmer's test, due to age-related glandular involution, may be less useful than ocular staining score as a confirmation test for keratoconjunctivitis sicca in EOpSS patients. LSG biopsy is performed less frequently in older patients, and there is a need to achieve a consensus among experts on how to differentiate pSS lesions from the age-related degenerative and atrophic lesions of salivary glands. Futhermore, the relationship between EOpSS and cancer risk must be evaluated through further studies on ad hoc cohorts, taking into account that age is one of the most important risk factors for the development of malignancies. Lastly, the specificity and sensitivity of AECG criteria should be evaluated in a comparative way between

older and younger age groups; currently, this evaluation is scarcely considered. Additionally, no data are available on EOpSS regarding the specificity and sensitivity of the criteria proposed in 2016 by the ACR/EULAR collaborative group.

References

1. Pontarini E et al. Current views on the pathogenesis of Sjögren's syndrome. Curr Opin Rheumatol. 2018;30(2): 215-21.
2. Nocturne G, Mariette X. B cells in the pathogenesis of primary Sjögren syndrome. Nat Rev Rheumatol. 2018;14(3):133-45.
3. Toussirot E, Roudier J. Epstein-Barr virus in autoimmune diseases. Best Practice Res Clin Rheumatol. 2008;22(5):883-96.
4. Yin Q et al. Ultraviolet B irradiation induces skin accumulation of plasmacytoid dendritic cells: A possible role for chemerin. Autoimmunity. 2014;47(3):185-92.
5. Tzioufas AG et al. Neuroendocrine dysfunction in Sjogren's syndrome. Neuroimmunomodulation. 2008;15(1):37-45.
6. Hayashi Y et al. Apoptosis and estrogen deficiency in primary Sjögren syndrome. Curr Opin Rheumatol. 2004;16(5):522-6.
7. Olsson P et al. Cigarette smoking and the risk of primary Sjögren's syndrome: A nested case control study. Arthritis Res Ther. 2017;19:50.
8. Stone DU et al. Effect of tobacco smoking on the clinical, histopathological, and serological manifestations of Sjögren's syndrome. PLoS One. 2017;12(2):e0170249.
9. Maslinska M et al. Sjögren's syndrome: Still non fully understood disease. Rheumatol Int. 2015;35:233-41.
10. Qin B et al. Epidemiology of primary Sjogren's syndrome: A systematic review and meta-analysis. Ann Rheum Dis. 2015;74(11):1983-9.
11. Patel R, Shahane A. The epidemiology of Sjögren's syndrome. Clin Epidemiol. 2014;6:247-55.
12. Kabasakal Y et al. The prevalence of Sjögren's syndrome in adult women. Scand J Rheumatol. 2006;359(5): 379-83.
13. Drosos AA et al. Prevalence of primary Sjögren's syndrome in an elderly population. Br J Rheumatol. 1988;27(2):123-7.
14. Haugen AJ et al. Estimation of the prevalence of primary Sjögren's syndrome in two age-different community-based populations using two sets of classification criteria: The Hordaland Health Study. Scand J Rheumatol. 2008;37(1):30-4.
15. Botsios C et al. Elderly onset of primary Sjögren symdrome: Clinical manifestations, serological features and oral/ocular diagnostic tests. Comparison with adult and young onset of the disease in a cohort of 336 Italian patients. Joint Bone Spine. 2011;78(2):171-4.
16. Chebbi W et al. Primitive Sjögren syndrome in the elderly: Clinical and immunological characteristics. Pan Afr Med J. 2015;20:8. [In French].
17. Johansson AK et al. Self-reported dry mouth in Swedish population samples aged 50, 65 and 75 years. Gerodontology. 2012;29(2):e107-15.
18. Lin PY et al. Prevalence of dry eye among an elderly Chinese population in Taiwan: The Shihpai Eye Study. Ophthalmology. 2003;110(6):1096-101.
19. Flament T et al. Pulmonary manifestations of Sjögren's syndrome. Eur Respir Rev. 2016;25(140):110-23.
20. Manfredi A et al. Prevalence and characterization of non-sicca onset primary Sjogren syndrome with interstitial lung involvement. Clin Rheumatol. 2017;36:1261-8.
21. Vitali C et al. Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum. 1993;36(3):340-7.
22. Vitali C et al. Classification criteria for Sjögren's syndrome: A revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002;61(6):554-8.
23. Shiboski CH et al. 2016 American College of Rheumatology/European League against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. Arthritis Rheumatol. 2017;69(1):35-45.
24. Vitali C, Del Papa N. Classification and diagnostic criteria in Sjogren's syndrome: A long-standing and still open controversy. Ann Rheum Dis. 2017;76(12):1953-4.
25. Baer AN, Walitt BW. Sjögren syndrome and other causes of sicca in the older adult. Clin Geriatr Med. 2017;33(1):87-103.
26. Odzemir M, Temizdemir H. Age- and gender related tear function in normal population. Eye. 2010;24(1):79-83.
27. Wolff A et al. A guide to medications inducing salivary gland dysfunction, xerostomia, and subjective sialorrhea: A systematic review sponsored by the World Workshop on Oral Medicine VI. Drugs R D. 2017;17(1):1-28.
28. Dirix P et al. Radiation-induced xerostomia in patients with head and neck cancer: A literature review. Cancer. 2006;107(11):2525-34.
29. Haddad J et al. Lymphocytic sialadenitis of Sjögren's syndrome associated with chronic hepatitis C virus liver disease. Lancet. 1992;339(8789):321-3.
30. Daniels TE et al. Association between salivary gland histopathologic diagnoses and phenotypic features of Sjögren's syndrome among 1,726 registry participants. Arthritis Rheum. 2011;63(7):2021-30.
31. Fisher BA et al. Standardisation of labial salivary gland histopathology in clinical trials in primary Sjögren's syndrome. Ann Rheum Dis. 2017;76(7):1161-8.
32. Fulop T et al. Immunosenescence and inflammaging as two sides of the same coin: Friends or foes? Front Immunol. 2018;8:1960.
33. Bouma HR et al. Aging and immunopathology in primary Sjögren's syndrome. Curr Aging Sci. 2015;8(2):202-13.
34. Tong L et al. Review of autoantigens in Sjogren's syndrome: An update. J Inflamm Res. 2017;10:97-105.
35. Grönwall C et al. IgM autoantibodies to distinct apoptosis-associated antigens correlate with protection from cardiovascular events and renal disease in patients with SLE. Clin Immunol. 2012;142(3):390-8.
36. Haga HJ, Jonsson R. The influence of age on disease manifestations and serological characteristics in primary Sjögren's syndrome. Scand J Rheumatol. 1999;28(4):227-32.
37. Tishler M et al. Clinical and immunological characteristics of elderly onset Sjögren's syndrome: A comparison with younger onset disease. J Rheumatol. 2001;28(4): 795-7.
38. Ingegnoli F et al. Rheumatoid factors: Clinical applications. Dis Markers. 2013;35(6):727-34.
39. Liang Y et al. Primary Sjögren's syndrome and malignancy risk: A systematic review and meta-analysis. Ann Rheum Dis. 2014;73(6):1151-6.
40. Manzo C, Kechida M. Is primary Sjogren's syndrome a risk factor for malignancies different from lymphomas? What does the literature highlight about it? Reumatologia. 2017;55(3):136-9.
41. Gadalla SM et al. Breast cancer in elderly women with systemic autoimmune rheumatic diseases: A population-based case-control study. Br J Cancer. 2009;100(5):817-21.
42. García-Carrasco M et al. Primary Sjögren syndrome: Clinical and immunologic disease patterns in a cohort of 400 patients. Medicine (Baltimore). 2002;8(4):270-80.

Cytokines and Inflammatory Mediators in Systemic Lupus Erythematosus

Authors: Manuel Rojas, Yhojan Rodríguez, Kelly Joan Leon, Yovana Pacheco, Yeny Acosta-Ampudia, Diana M. Monsalve, Carolina Ramírez-Santana, *Juan-Manuel Anaya

Center for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia
*Correspondence to juan.anaya@urosario.edu.co

Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: The authors would like to thank their colleagues at CREA for their fruitful discussions and contributions. This work was supported by Universidad del Rosario (ABN011), and Colciencias (122254531722), Bogotá, Colombia.

Received: 06.03.18

Accepted: 24.05.18

Keywords: Biomarkers, cytokines, inflammation, inflammatory mediators, systemic lupus erythematosus (SLE).

Citation: EMJ Rheumatol. 2018;5[1]:83-92.

Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by a breakdown in immune tolerance that induces an attack on normal tissues by the immune system. The dysfunction within both the innate and adaptive immune systems increases cytokine production, B lymphocytic overproduction of autoantibodies, and T lymphocyte activity. Cytokines and inflammatory mediators have been associated with several clinical endpoints, including the activity of disease and outcomes. In fact, some of them have been associated with different clinical subphenotypes (e.g., lupus nephritis), suggesting their role as biomarkers, and, in some cases, therapeutic targets. Thus, knowledge of the pathophysiological processes associated with the development of SLE could aid in setting up better diagnostic and therapeutic approaches to reduce the high burden of disease, and thus improve quality of life and outcomes. Herein, the authors have compiled a concise review of the clinically relevant cytokines and inflammatory mediators associated with SLE and its manifestations.

INTRODUCTION

Systemic lupus erythematosus (SLE) is the prototypical autoimmune disease (AD), with a prevalence of up to 178 per 100,000 habitants, with an increased incidence and severity in non-Caucasian patients.[1] Patients typically show burdensome symptoms of psychological distress and a marked effect on physical function that impairs their quality of life.[2] Clinical manifestations include arthritis, rash, serositis, cytopenia, kidney disease, and neurological involvement.[3]

SLE is characterised by the dysfunction of both the innate and adaptive immune systems, which increase the production of cytokines and other inflammatory mediators (Figure 1).[4] These molecules produce a strengthening of inflammatory responses, an increase in the

apoptosis of circulating cells, a defect in clearing apoptotic bodies, and an overproduction of autoantibodies, which are associated with diverse clinical subphenotypes. New biomarkers, such as soluble urokinase plasminogen activator receptor (suPAR), osteopontin, and soluble Fas (sFas), have arisen as valuable tools to measure activity and severity of disease.[5-7] However, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels remain the most useful tools to evaluate activity of disease.[8]

Cytokines and several inflammatory mediators are integrated in a complex network of biological elements, including genetic polymorphisms and environmental factors.[9] Studies of the interactions between these variables from a systems medicine perspective could therefore provide a better understanding of the pathological mechanisms associated with the development of SLE. In this regard, Pacheco et al.[10] found that some cytokine and autoantibody clusters (i.e., neutral, chemotactic/antiphospholipid antibodies, and Type 1 IFN-α/double-stranded DNA [dsDNA]) were associated with activity of disease. Thus, the understanding of the mechanisms associated with development of SLE is pivotal for the development of new interventions and accurate diagnosis strategies. Herein, the authors provide a summary of the most clinically relevant cytokines and inflammatory mediators associated with SLE.

CYTOKINES AND THE INNATE IMMUNE SYSTEM

Interleukin-1β

IL-1β is considered a multifunctional cytokine and belongs to the IL-1 family, a group of 11 cytokines, which plays a central role in the regulation of immune and inflammatory responses. IL-1β is characterised by highly inflammatory properties that may have a significant effect on disease.[9] IL-1β is produced in response to inflammasome activation, which is commonly defined as a group of intracellular multiprotein signalling complexes associated with inflammatory responses to extracellular pathogens.[11]

It has been recognised that IL-1β levels are increased in patients with SLE, especially in individuals with systemic manifestations, such as fever.[12] The activation of the inflammasome has been proposed as a mechanism in SLE pathophysiology, which includes the stimulation of toll-like receptors (TLR) and NF-κβ transcription by immune complexes or C3a.[13]

Polymorphisms of the *IL1* gene have been associated with SLE development.[14] IL-1β-deficient mice are resistant to induction of experimental SLE.[15] Furthermore, IL-1β expression and IL-1 levels are increased in the kidneys of mice with lupus nephritis (LN).[16] These data advocate for a plausible role of this cytokine in the development of LN, which may function as a diagnostic biomarker and therapeutic target in this subset of patients.[17] Anakinra, an IL-1R antagonists, has been shown to be safe and well-tolerated in patients with severe lupus arthritis.[18] However, the efficacy of this treatment is poor and the studies only include a low number of patients; thus, further studies are warranted to clarify the usefulness of this treatment in patients with SLE.

Interleukin-8

IL-8 is a potent neutrophil chemokine that has been previously associated with renal injury in humans.[19] It has been found that IL-8 induces neutrophil recruitment and extracellular trap formation (NETosis), increasing the risk of antinuclear autoantibody production,[20] suggesting it plays a role in the early stages of SLE.

IL8-845C polymorphism has been associated with an increased risk of LN in African Americans.[19] Indeed, urine levels of IL-8 are associated with activity of SLE and LN.[21] Furthermore, IL-8 concentrations in cerebrospinal fluid from patients with neuropsychiatric lupus were found to be higher than in healthy donors, and inflammatory mediators, such as IL-6, IP-10, and MCP-1, were simultaneously elevated, suggesting the existence of a complex interaction network among these inflammatory mediators and the development of neuropsychiatric lupus.[22] Since long-term treatment of SLE with standard immunomodulatory drug regimens failed to normalise levels of key chemoattractant proteins linked to innate immunity, including IL-8,[23] blockade of IL-8 could be considered a plausible therapeutic target in SLE.

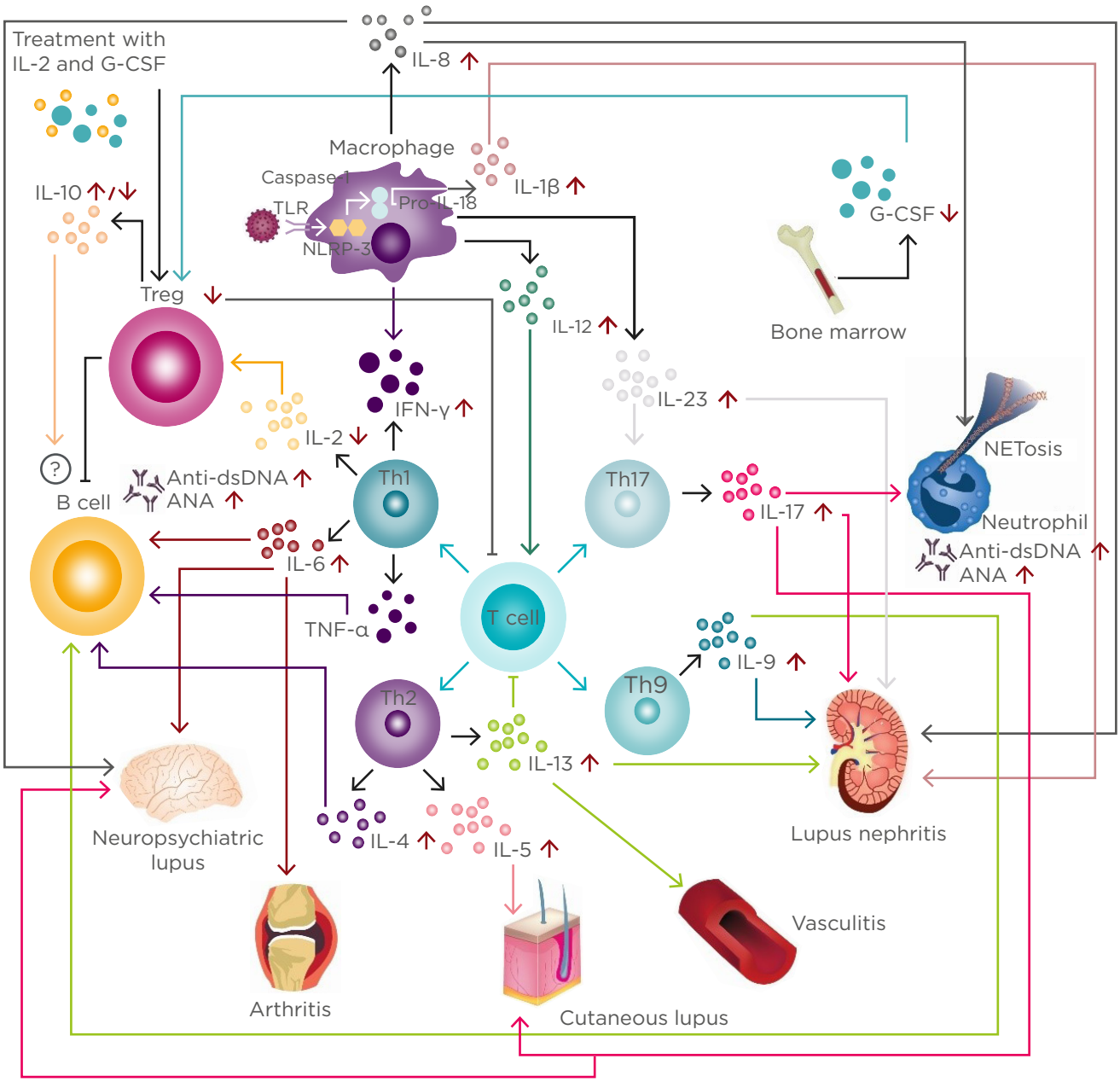


Figure 1: Cytokine network in systemic lupus erythematosus.

T cell response: Immune activation secondary to infections and other harmful agents triggers T cell responses inducing the differentiation of different T cell populations, such as Th1, Th2, Th9, and Th17.

B cell response: IL-4, IL-6, IL-9, and TNF-α produced by T cells increases the production of anti-dsDNA and ANA. Although IL-10 is considered a regulatory cytokine, its role on B cells is not fully understood.

Innate immune response: Activation of the inflammasome induces the production of IL-1β, which, together with IL-17, is associated with the induction of NETosis. Further, IFN-γ, IL-12, and IL-23 are associated with the enhancement of T cell responses, increasing the inflammatory process.

Modulatory immune response: IL-2 and G-CSF levels are decreased in patients with SLE, correlating with a reduction of Treg. Currently, clinical trials with IL-2 and G-CSF are underway.

SLE subphenotypes: Cytokines and innate and T cell responses influence the development of lupus nephritis, vasculitis, cutaneous lupus, arthritis, and neuropsychiatric SLE.

ANA: antinuclear antibodies; dsDNA: double-stranded DNA antibodies; G-CSF: granulocyte colony-stimulating factor; IFN: interferon; IL: interleukin; NETosis: neutrophil recruitment and extracellular trap formation; TLR: toll-like receptor; NLPR-3: NACHT, LRR, and PYD domains-containing protein 3; SLE: systemic lupus erythematosus; Th: T helper; TNF: tumour necrosis factor; Treg: T regulatory cells.

Interleukin-12 and 23

The IL-12 family includes IL-12, IL-23, IL-27, and IL-35. These cytokines are critical for Th1 differentiation and play a major role as proinflammatory mediators.[24] In a study conducted by Qiu et al.,[24] patients with SLE showed high levels of these cytokines and were correlated with anti-dsDNA antibodies. The serum p40 monomer concentration of IL-12 was elevated in the sera of patients and correlated with the activity of disease.[25] Clinical trials with IL-12p40 antagonist (ustekinumab) are underway.[26]

Regarding IL-23, patients with active disease showed higher IL-23 mRNA compared with patients with inactive disease, as well as healthy controls. Furthermore, IL-23 levels were significantly higher in patients with renal compromise.[27,28] Further to this, mice treated with a neutralising anti-IL-23 antibody had less severe nephritis than control-treated mice, suggesting that IL-23 plays a role in the development of autoimmunity and ensuing inflammation in SLE.[29] *In vitro* IL-23 treatment promotes IL-17 production and downregulates IL-2 production. The *IL-23R* knockdown mouse model presented fewer T follicular helper lymphocytes, B lymphocytes, and plasma cells, leading to decreased production of anti-dsDNA antibody.[30,31] Similar to IL-12, clinical trials with IL-23 blockers (briakinumab) are ongoing.[26]

TYPE 1 T HELPER CELL RESPONSE AND SYSTEMIC LUPUS ERYTHEMATOSUS

Interleukin-2

IL-2 is an auto and paracrine growth factor for both T and B lymphocytes. This cytokine is considered an essential growth and survival factor for regulatory T lymphocytes (Treg).[32] Nevertheless, it has been found that IL-2 downregulates the expansion of T follicular regulatory cells, thus suggesting the pleotropic role of this cytokine in immune responses and encouraging studies about the role of follicular IL-2 on SLE.[32]

It has been shown that lymphocytes from patients with SLE produce low levels of IL-2 that may trigger low counts of Tregs.[33] This low production has been associated with active repression of *IL-2* transcription mediated by the binding of phosphorylated CREM to the IL-2 promoter.[32] In a study by Schorle et al.,[34] *IL-2/IL-2R* knockdown mice showed SLE hallmarks, such as autoantibody production, lymphadenopathy, and decreased Treg lymphocytes. Recently, He et al.[35] found that treatment with a low dose of recombinant human IL-2 selectively modulated the abundance of Treg lymphocytes, but not Th1 or Th2, and was accompanied by marked reductions in SLE disease activity.

Interleukin-6

IL-6 is a pleiotropic cytokine synthesised predominantly by monocytes, fibroblasts, endothelial cells, and less frequently in T and B lymphocytes. This cytokine induces the maturation of B lymphocytes and increases Ig secretion.[36] The role of this cytokine in SLE has been widely studied and, in some cases, has been associated with SLE subphenotypes and disease activity.

It has been described that *IL6-174G/C* and *IL6-572G/C* polymorphisms are associated with the development of SLE.[37] Talaat et al.[38] found that patients with SLE showed higher levels of IL-6 than controls and that IL-6 was associated with activity of disease. Patients with lupus arthritis also showed high levels of IL-6, which, in turn, correlated with high anti-dsDNA antibody and ESR levels.[39] A recent clinical trial reported by Illei et al.[40] found that patients with SLE and arthritis who were treated with an IL-6 blocker (i.e., tocilizumab) exhibited an improvement of symptoms and some showed remission. Furthermore, patients treated with rituximab after B cell repopulation can be divided into two groups: those responding to rituximab (responders) and those not responding to rituximab (non-responders). Non-responding patients showed an increase in the expression of TNF-α and IL-6, and a reduction in CD24+ $CD38^{high}$ regulatory B cells compared to healthy controls and responders.[41] All together, these data indicate IL-6 is a therapeutic target in SLE.

Tumour Necrosis Factor-α

TNF-α is a cytokine from a group of 15 proteins belonging to the TNF family. There are two active forms of the TNF-α protein, a membrane-bound form and a soluble form, and it is produced by a large group of immune cells, such as macrophages, T and B lymphocytes,

natural killer cells, neutrophils, and astrocytes.[42] TNF is considered a growth factor for B lymphocytes, inducing secretion of IL-1 and IL-6 and a triggering factor for the activation and proliferation of T lymphocytes.[43]

Controversial results in SLE have been found for TNF-α. Increased plasma levels of TNF-α were associated with immunomodulatory activity reducing severity but have also been linked to deleterious effects and increased disease activity.[44-46] Indeed, TNF-α antagonists induce SLE-like disease, suggesting TNF-α is beneficial in a SLE context. Further studies are therefore warranted to clarify the role of TNF antagonists from a personalised medicine approach.

Interferon-α

IFN-α belongs to the Type I IFN family, which are glycoproteins known for their capacity to interfere in viral infections. The upregulation of the expression of these genes in SLE patients has been called the IFN-α signature.[47] This cytokine has been associated with an increased number of plasma lymphocytes, autoantibody production, defective apoptotic cell clearance, and promotion of T cell-dependent inflammation.[48] Three mechanisms of IFN-α response have been described. The first involves NETosis and the creation of an interferogenic signal mediated by TLR-7 or TLR-9. The second refers to the contribution of an extensive proportion of AD genetic risk variants that can affect IFN-α production.[49] The third mechanism denotes a chronic dysregulation of plasmacytoid dendritic cells that induce an increase of IFN-α secretion.[50,51] In murine models, the IFN-α pathway blockade is associated with better outcomes.[52] Currently, promising anti-IFN-α monoclonal antibodies (i.e., sifalimumab and anifrolumab) are under clinical study.[53]

Interferon-γ

This cytokine is included in the Type II IFN group. Macrophages, natural killer cells, and T lymphocytes, especially CD4+ and CD8+ T lymphocytes, secrete IFN-γ. IFN-γ activates macrophages at the site of inflammation, contributes to cytotoxic T lymphocytes activity, has antiviral capacities, and has been strongly associated with Th1 response.[47,54] Patients and murine models of SLE typically show high levels of this cytokine, and blockade abrogates SLE development in mice.[9,55] An anti-IFN-γ monoclonal antibody is under development with promising results.[56]

TYPE 2 T HELPER CELL RESPONSE AND SYSTEMIC LUPUS ERYTHEMATOSUS

Interleukin-4

IL-4 is a pleiotropic cytokine characterised by the stimulation of CD4+ T lymphocytes to differentiate into Th2 and the inhibition of Th1-type cytokine production.[57] It has been proposed that IL-4's role in rescuing B cells from apoptosis may promote autoreactive B lymphocyte survival in mouse models.[58] IL-4 treatment triggered the production of IgG anti-dsDNA antibody, and the blockade of IL-4 prevents the onset of LN.[58] Furthermore, in SLE murine models, the IL-4 knockout mice produced less IgG1 and IgE serum Ig,[59] thus suggesting a major role of this cytokine in the pathogenesis of disease.

However, evidence is conflicting, and some patients with cutaneous and articular manifestations showed low levels of IL-4,[60] commonly due to an imbalance of IFN-γ/IL-4-producing CD4+ T lymphocytes.[61] This ratio correlates with the activity of disease and is significantly higher among patients with LN.[61]

Interleukin-5

IL-5 is preferentially produced by Th2 lymphocytes. It is considered a growth and differentiation factor of eosinophils and B lymphocytes.[62] Zhu et al.[63] described that patients with LN and high activity of disease showed higher levels of IL-5 than controls. Furthermore, patients with severe or extensive skin lesions showed an overexpression of IL-5, suggesting that Th2 lymphocytes are involved in SLE skin inflammation.[64] On the other hand, Timóteo et al.[65] reported lower levels of IL-5 in patients with SLE than controls; however, these patients showed low activity of disease.

In murine models, the high expression of IL-5 may directly or indirectly mediate a skewed signalling of proliferation and differentiation of self-antigen-activated B lymphocytes, leading to suppression of AD.[62] These data suggest that different concentrations of the cytokine

could play a role in the development of SLE and the expression of diverse subphenotypes.

Interleukin-13

IL-13 is considered a strong anti-inflammatory cytokine, with modulatory properties that include the modulation of macrophages, monocytes, and B lymphocytes. Conversely, it has been found that patients with SLE showed high levels of this cytokine, especially in those with LN,[66] thus suggesting a failure in immunomodulatory function of IL-13 in patients with SLE. In murine models, T lymphocytes infiltrating the glomeruli and perivascular areas predominantly produced IFN-γ, IL-13, and IL-17. Thus, IL-13 may also be an important factor in the pathogenesis of glomerulonephritis and vasculitis.[67]

Furthermore, increased CD38 expression in SLE T lymphocytes correlated with plasma levels of IL-13, and positively correlated with activity of disease, ESR, and serum levels of C3.[68,69] DNA methylation levels within the *IL10* and *IL13* gene regulatory domains are reduced in SLE CD4+ T cells relative to healthy controls, and negatively correlate with *IL10* and *IL13* mRNA expression.[70]

TYPE 9 T HELPER CELL RESPONSE AND SYSTEMIC LUPUS ERYTHEMATOSUS

Interleukin-9

IL-9 is a T cell-derived factor preferentially expressed by CD4+ T lymphocytes with inflammatory properties. It has been found that patients with SLE showed high levels of IL-9 and the proportion of CD4+ IL-9-producing CD4+ T lymphocytes correlates with disease activity, proteinuria, low C3 titres, and high severity of disease.[71,72] Similarly to IL-6, active patients who were treated and achieved disease control showed a reduction in IL-9 concentrations.[73]

Lupus-prone mice have shown an increased production of IL-9 and an expansion of Th9 lymphocytes, which were associated with anti-dsDNA antibody. In addition, IL-9 appears to promote B lymphocyte proliferation and autoantibody production, which could be blocked by inhibition of signal transducer STAT3. Indeed, IL-9 blockade reduced serum anti-dsDNA antibody titres and lessened renal disease.[74]

TYPE 17 T HELPER CELL RESPONSE AND SYSTEMIC LUPUS ERYTHEMATOSUS

Interleukin-17

IL-17 is a proinflammatory cytokine produced by activated T lymphocytes with a high influence to recruit monocytes and neutrophils.[36] IL-17 can amplify the immune response by increasing the production of autoantibodies through the stimulation of B lymphocytes.[75]

Patients with SLE usually show high levels of IL-17A;[76] in fact, the IL-17A serum levels positively correlate with activity of disease.[77] Different subphenotypes have been associated with high levels of IL-17, including cutaneous, haematological, and central nervous system compromise.[78,79] Furthermore, it has been shown that IL-17 is associated with LN and increased anti-dsDNA autoantibody production.[80] The first report of an effective IL-17-targeted therapy in SLE was published recently.[81]

T REGULATORY CELLS AND SYSTEMIC LUPUS ERYTHEMATOSUS

Interleukin-10

IL-10 is a cytokine produced mainly by Treg cells and regulates the immune response; however, IL-10 improves B lymphocyte proliferation and Ig class switching, increasing antibody secretion.[36] It has been described that patients with SLE showed high levels of IL-10, which were positively correlated with activity of disease and anti-dsDNA antibody, and negatively correlated with C3 and C4 levels, as well as with lymphocyte counts.[82] In murine models, the IL-10 blockade limited the renal damage and decreased the production of anti-dsDNA antibodies.[83]

MRL-Fas(lpr) IL-10 knockout mice developed severe lupus, with earlier appearance of skin lesions, increased lymphadenopathy, more severe glomerulonephritis, and higher mortality than their IL-10-intact littermate controls.[84] The increased severity of lupus in MRL-Fas(lpr) IL-10 knockout mice was closely associated with enhanced IFN-γ production by both CD4+ and CD8+ lymphocytes and increased serum concentration of IgG2a anti-dsDNA

autoantibodies.[84] Administration of the recombinant IL-10 reduced IgG2a anti-dsDNA autoantibody production in wild-type MRL-Fas(lpr) animals, supporting the protective effect of IL-10.[84]

In short, a pathogenic role for IL-10 appears to predominate and affect many facets of SLE, and its blockade is likely to prove an effective therapeutic strategy. However, no current clinical trials aiming to directly block IL-10 have been published.

OTHER INFLAMMATORY MEDIATIORS IN SYSTEMIC LUPUS ERYTHEMATOSUS

Erythrocyte Sedimentation Rate and C-Reactive Protein in Systemic Lupus Erythematosus

ESR and CRP are the oldest and most widely used biomarkers of systemic inflammation and tissue injury. Although CRP is replacing ESR as an inflammatory biomarker due to its high sensitivity and specificity, ESR remains a useful tool for diagnosis or monitoring of disease activity in SLE.[8]

ESR appears to be a reliable marker (with cut-off above 25–30 mm/h) for disease activity assessment in non-infected SLE patients. On the other hand, CRP >10 mg/L in noninfected patients could be indicative of disease severity. Additionally, in the absence of serositis or arthritis, a significantly increased CRP (>50–60 mg/L) is generally associated with infection.[8]

Osteopontin

Osteopontin is a pleiotropic protein that affects bone remodelling and immune system signalling. It plays a key role in regulating Th1/Th2 balance, stimulating B lymphocytes to produce antibodies, regulating macrophages and neutrophils, and inducing activation of dendritic cells. Overexpression of osteopontin has been associated with the pathogenesis of AD such as SLE.[5] Recently, osteopontin-full and osteopontin N-half (cleaved from osteopontin-full) were measured in the serum and urine of SLE patients. In this study,[85] osteopontin N-half in urine was higher in LN than in healthy controls. In addition, osteopontin N-half in urine decreased after the treatment of LN, suggesting that osteopontin N-half in urine could be a biomarker for evaluating activity of the disease. This data was confirmed in a meta-analysis, which revealed a significantly higher circulating osteopontin level in SLE patients, a trend of positive correlation between osteopontin levels and SLE activity, and a significant association between osteopontin gene 1239C>A and 9250C>T polymorphisms with SLE development.[86]

Soluble Urokinase-Type Plasminogen Activator Receptor

The soluble urokinase-type plasminogen activator receptor (suPAR) has been described as a valuable indicator of activity in the immune system. SuPAR is expressed in smooth muscle and endothelial cells.[87] An inflammatory response leads to elevated suPAR levels, as reported in AD.[88]

Circulating suPAR has emerged as a potential marker of inflammation and disease severity in SLE. Recently, Enocsson et al.[6] evaluated suPAR as a marker of disease activity and organ damage in SLE. The study found that suPAR levels were significantly elevated in patients with SLE compared to healthy controls. Furthermore, a strong association was detected between suPAR and severity of disease.[6]

Soluble Fas and Fas Ligand in Systemic Lupus Erythematosus

Fas and Fas ligand are members of the TNF and TNF-receptor families that are involved in apoptosis. The Fas receptor exists in two forms: one is attached to the plasma membrane, whereas the other is soluble (sFas). The latter is associated with anti-apoptotic functions.[89] In SLE, sFas levels are increased due to a deletion in exon 6, and this increase has been associated with LN.[7,90] Hatef et al.[7] reported a significant rise in the serum concentrations of sFas and IL-18 in patients with proteinuria compared to those without it. Moreover, this study showed that the correlation between sFas and IL-18 in LN was significantly stronger than in mild SLE with similar non-renal SLE Disease Activity Index score.

CONCLUSION

Cytokines and inflammatory mediators are key factors for the development of SLE. As discussed in this review, cytokines are associated with diverse clinical manifestations

(i.e., clinical subphenotypes), and some of them have been associated with activity and severity of disease. This suggests that cytokine profiles, if used as biomarkers, could aid in the monitoring and treatment of disease. However, it is necessary to recognise that these inflammatory mediators are associated with other biological variables that could reduce or increase their impact on different biological levels. Thus, additional studies to clarify those complex interactions are warranted. With the exception of belimumab, no Phase III trials of biologic therapy in SLE have met their primary endpoint. However, the significant steroid-sparing effect of these agents suggests that future trials may need to include steroid dose in a composite primary endpoint.[91]

References

1. Stojan G et al. Epidemiology of systemic lupus erythematosus: An update. Curr Opin Rheumatol. 2018;30(2):144-50.
2. Björk M et al. Quality of life and acquired organ damage are intimately related to activity limitations in patients with systemic lupus erythematosus. BMC Musculoskelet Disord. 2015;16(1):188.
3. Agmon-Levin N et al. Systemic lupus erythematosus one disease or many? Autoimmun Rev. 2012;11(8):593-5.
4. Gurevitz SL et al. Systemic lupus erythematosus: A review of the disease and treatment options. Consult Pharm. 2013;28(2):110-21.
5. Kaleta B. Role of osteopontin in systemic lupus erythematosus. Arch Immunol Ther Exp (Warsz). 2014;62(6):475-82.
6. Enocsson H et al. Soluble urokinase plasminogen activator receptor levels reflect organ damage in systemic lupus erythematosus. Transl Res. 2013;162(5):287-96.
7. Hatef MR et al. Stronger correlation between interleukin 18 and soluble fas in lupus nephritis compared with mild lupus. ISRN Rheumatol. 2013;2013:850851.
8. Dima A et al. Is there still a place for erythrocyte sedimentation rate and C-reactive protein in systemic lupus erythematosus? Lupus. 2016;25(11):1173-9.
9. Guimarães PM et al. Cytokines in systemic lupus erythematosus: Far beyond Th1/Th2 dualism lupus: Cytokine profiles. Immunol Cell Biol. 2017;95(9):824-31.
10. Pacheco Y et al. Cytokine and autoantibody clusters interaction in systemic lupus erythematosus. J Transl Med. 2017;15(1):239.
11. Awad F et al. Inflammasome biology, molecular pathology and therapeutic implications. Pharmacol Ther. 2018. [Epub ahead of print].
12. Yao Y et al. Balance between inflammatory and regulatory cytokines in systemic lupus erythematosus. Genet Mol Res. 2016;15(2):1-8.
13. Kahlenberg JM, Kaplan MJ. The inflammasome and lupus: Another innate immune mechanism contributing to disease pathogenesis? Curr Opin Rheumatol. 2014;26(5): 475-81.
14. Song GG et al. Associations between interleukin 1 polymorphisms and susceptibility to systemic lupus erythematosus: A meta-analysis. Hum Immunol. 2014;75(1):105-12.
15. Voronov E et al. IL-1 beta-deficient mice are resistant to induction of experimental SLE. Eur Cytokine Netw. 2006;17(2):109-16.
16. Boswell JM et al. Novel and enhanced IL-1 gene expression in autoimmune mice with lupus. J Immunol. 1988;141(1):118-24.
17. Cigni A et al. Interleukin 1, interleukin 6, interleukin 10, and tumor necrosis factor α in active and quiescent systemic lupus erythematosus. J Investig Med. 2014;62(5):825-9.
18. Ostendorf B et al. Preliminary results of safety and efficacy of the interleukin 1 receptor antagonist anakinra in patients with severe lupus arthritis. Ann Rheum Dis. 2005;64(4):630-3.
19. Rovin BH et al. A novel interleukin-8 polymorphism is associated with severe systemic lupus erythematosus nephritis. Kidney Int. 2002;62(1): 261-5.
20. Gupta AK et al. Efficient neutrophil extracellular trap induction requires mobilization of both intracellular and extracellular calcium pools and is modulated by cyclosporine A. PLoS One. 2014;9(5):e97088.
21. El-Shehaby A et al. Correlations of urinary biomarkers, TNF-like weak inducer of apoptosis (TWEAK), osteoprotegerin (OPG), monocyte chemoattractant protein-1 (MCP-1), and IL-8 with lupus nephritis. J Clin Immunol. 2011;31(5):848-56.
22. Yoshio T et al. IL-6, IL-8, IP-10, MCP-1 and G-CSF are significantly increased in cerebrospinal fluid but not in sera of patients with central neuropsychiatric lupus erythematosus. Lupus. 2016;25(9):997-1003.
23. Vega L et al. Prolonged standard treatment for systemic lupus erythematosus fails to normalize the secretion of innate immunity-related chemokines. Eur Cytokine Netw. 2010;21(1):71-6.
24. Qiu F et al. Glucocorticoid downregulates expression of IL-12 family cytokines in systemic lupus erythematosus patients. Lupus. 2013;22(10):1011-6.
25. Lauwerys BR et al. Serum IL-12 in systemic lupus erythematosus: Absence of p70 heterodimers but presence of p40 monomers correlating with disease activity. Lupus. 2002;11(6):384-7.
26. Teng MWL et al. IL-12 and IL-23 cytokines: From discovery to targeted therapies for immune-mediated inflammatory diseases. Nat Med. 2015;21(7):719-29.
27. ElGlil RR et al. Expression of IL-23 mRNA in systemic lupus erythramtosus patients: Relation with disease Activity. Egypt J Immunol. 2015;22(2):9-21.
28. Du J et al. Associations between serum interleukin-23 levels and clinical characteristics in patients with systemic lupus erythematosus. J Int Med Res. 2014;42(5):1123-30.
29. Kyttaris VC et al. Treatment with anti-interleukin 23 antibody ameliorates disease in lupus-prone mice. Biomed Res Int. 2013;2013:861028.
30. Dai H et al. IL-23 limits the production of IL-2 and promotes autoimmunity in lupus. J Immunol. 2017;199(3):903-10.
31. Shaltout AS et al. Effect of IL6 and IL23 on double negative T cells and anti ds-DNA in systemic lupus erythematosus patients. Hum Immunol. 2016;77(10):937-43.
32. Solomou EE et al. Molecular basis of deficient IL-2 production in T cells from patients with systemic lupus erythematosus. J Immunol. 2001;166(6):4216-22.
33. Linker-Israeli M et al. Defective production of interleukin 1 and interleukin 2 in patients with systemic lupus erythematosus (SLE). J Immunol. 1983;130(6):2651-5.

34. Schorle H et al. Development and function of T cells in mice rendered interleukin-2 deficient by gene targeting. Nature. 1991;352(6336): 621-4.

35. He J et al. Low-dose interleukin-2 treatment selectively modulates CD4(+) T cell subsets in patients with systemic lupus erythematosus. Nat Med. 2016;22(9):991-3.

36. Yap DYH, Lai KN. Cytokines and their roles in the pathogenesis of systemic lupus erythematosus: from basics to recent advances. J Biomed Biotechnol. 2010;2010:365083.

37. Cui YX et al. Association of the interleukin-6 polymorphisms with systemic lupus erythematosus: A meta-analysis. Lupus. 2015;24(12):1308-17.

38. Talaat RM et al. Th1/Th2/Th17/Treg cytokine imbalance in systemic lupus erythematosus (SLE) patients: Correlation with disease activity. Cytokine. 2015;72(2):146-53.

39. Eilertsen GØ et al. Interleukin-6 promotes arthritis and joint deformation in patients with systemic lupus erythematosus. Lupus. 2011;20(6):607-13.

40. Illei GG et al. Tocilizumab in systemic lupus erythematosus: Data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label Phase I dosage-escalation study. Arthritis Rheum. 2010;62(2):542-52.

41. Menon M et al. A regulatory feedback between plasmacytoid dendritic cells and regulatory B cells is aberrant in systemic lupus erythematosus. Immunity. 2016;44(3):683-97.

42. Doss GPC et al. TNF/TNFR: Drug target for autoimmune diseases and immune-mediated inflammatory diseases. Front Biosci (Landmark Ed.). 2014;19:1028-40.

43. Postal M et al. The role of tumor necrosis factor-alpha (TNF-α) in the pathogenesis of systemic lupus erythematosus. Cytokine. 2011;56(3):537-43.

44. Umare V et al. Effect of proinflammatory cytokines (IL-6, TNF-α, and IL-1β) on clinical manifestations in Indian SLE patients. Mediators Inflamm. 2014;2014:385297.

45. McCarthy EM et al. The association of cytokines with disease activity and damage scores in systemic lupus erythematosus patients. Rheumatology. 2014;53(9):1586-94.

46. Gómez D et al. Th1/Th2 cytokines in patients with systemic lupus erythematosus: Is tumor necrosis factor alpha protective? Semin Arthritis Rheum. 2004;33(6):404-13.

47. Mathian A et al. Targeting interferons in systemic lupus erythematosus: Current and future prospects. Drugs. 2015;75(8):835-46.

48. Pascual V et al. Systemic lupus erythematosus: All roads lead to type I interferons. Curr Opin Immunol. 2006;18(6):676-82.

49. Kariuki SN et al. Genetic regulation of serum cytokines in systemic lupus erythematosus. Transl Res. 2010;155(3):109-17.

50. Rönnblom L. The interferon signature in autoimmune diseases. Curr Opin Rheumatol. 2013;25(2):248-53.

51. Garcia-Romo GS et al. Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. Sci Transl Med. 2011;3(73):73ra20.

52. Baccala R et al. Anti-IFN-α/β receptor antibody treatment ameliorates disease in lupus-predisposed mice. J Immunol. 2012;189(12):5976-84.

53. Kalunian KC. Interferon-targeted therapy in systemic lupus erythematosus: Is this an alternative to targeting B and T cells? Lupus. 2016;25(10):1097-101.

54. Ohl K, Tenbrock K. Inflammatory cytokines in systemic lupus erythematosus. J Biomed Biotechnol. 2011;2011:432595.

55. Amital H et al. Immunomodulation of murine experimental SLE-like disease by interferon-gamma. Lupus. 1998;7(7):445-54.

56. Baker KF, Issacs JD. Novel therapies for immune-mediated inflammatory diseases: What can we learn from their use in rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and ulcerative colitis? Ann Rheum Dis. 2018;77(2):175-87.

57. Nakajima A et al. Roles of IL-4 and IL-12 in the development of lupus in NZB/W F1 mice. J Immunol. 1997;158(3):1466-72.

58. Deocharan B et al. Differential effects of interleukin-4 in peptide induced autoimmunity. Clin Immunol. 2003;108(2):80-8.

59. Peng SL et al. Roles of interferon-gamma and interleukin-4 in murine lupus. J Clin Invest. 1997;99(8): 1936-46.

60. Elewa EA et al. The role of interleukins 4, 17 and interferon gamma as biomarkers in patients with systemic lupus erythematosus and their correlation with disease activity. Egypt Rheumatol. 2014;36(1):21-7.

61. Sugimoto K et al. Decreased IL-4 producing CD4+ T cells in patients with active systemic lupus erythematosus-relation to IL-12R expression. Autoimmunity. 2002;35(6):381-7.

62. Wen X et al. Transgene-mediated hyper-expression of IL-5 inhibits autoimmune disease but increases the risk of B cell chronic lymphocytic leukemia in a model of murine lupus. Eur J Immunol. 2004;34(10):2740-9.

63. Zhu H et al. Whole-genome transcription and DNA methylation analysis of peripheral blood mononuclear cells identified aberrant gene regulation pathways in systemic lupus erythematosus. Arthritis Res Ther. 2016;18:162.

64. Carneiro JRM et al. IL-2, IL-5, TNF-α and IFN-γ mRNA expression in epidermal keratinocytes of systemic lupus erythematosus skin lesions. Clinics. 2011;66(1):77-82.

65. Timóteo RP et al. Characterization of inflammatory markers associated with systemic lupus erythematosus patients undergoing treatment. Rev Bras Reumatol. 2016;56(6):497-503.

66. Chen X et al. Elevated interleukin-13 in patients with active lupus nephritis. Chin Med J (Engl). 2001;114(10): 1022-5.

67. Guo Z et al. Use of laser microdissection in the analysis of renal-infiltrating T cells in murine lupus. Cent J Immunol. 2014;39(3):285-93.

68. Pavón EJ et al. Increased CD38 expression in T cells and circulating anti-CD38 IgG autoantibodies differentially correlate with distinct cytokine profiles and disease activity in systemic lupus erythematosus patients. Cytokine. 2013;62(2):232-43.

69. Xu Z et al. Determination of serum interleukin-13 and nerve growth factor in patients with systemic lupus erythematosus and clinical significance. J Huazhong Univ Sci Technol Med Sci. 2005;25(3):360-1.

70. Zhao M et al. Hypomethylation of IL10 and IL13 promoters in CD4+ T cells of patients with systemic lupus erythematosus. J Biomed Biotechnol. 2010;2010:1-9.

71. Ouyang H et al. Increased interleukin-9 and CD4+IL-9+ T cells in patients with systemic lupus erythematosus. Mol Med Rep. 2013;7(3):1031-7.

72. Rojas-Zuleta WG, Vásquez G. Th9 lymphocytes: A recent history from IL-9 to its potential role in rheumatic diseases. Autoimmun Rev. 2016;15(7):649-55.

73. Ciccia F et al. Interleukin-9 and T helper type 9 cells in rheumatic diseases. Clin Exp Immunol. 2016;185(2):125-32.

74. Yang J et al. Interleukin-9 Is associated with elevated anti-double-stranded DNA antibodies in lupus-prone mice. Mol Med. 2015;21(1): 364-70.

75. Li D et al. Interleukin-17 in systemic lupus erythematosus: A comprehensive review. Autoimmunity. 2015;48(6):353-61.

76. Bălănescu P et al. T helper 17 cell population in lupus erythematosus.

Rom J Intern Med. 2010;48(3):255-9.

77. Chen XQ et al. Plasma IL-17A is increased in new-onset SLE patients and associated with disease activity. J Clin Immunol. 2010;30(2):221-5.
78. Rana A et al. Gene expression of cytokines (TNF-α, IFN-γ), serum profiles of IL-17 and IL-23 in paediatric systemic lupus erythematosus. Lupus. 2012;21(10):1105-12.
79. Lu XY et al. Intrathecal cytokine and chemokine profiling in neuropsychiatric lupus or lupus complicated with central nervous system infection. Lupus. 2010;19(6):689-95.
80. Wen Z et al. Interleukin-17 expression positively correlates with disease severity of lupus nephritis by increasing anti-double-stranded DNA antibody production in a lupus model induced by activated lymphocyte derived DNA. PLoS One. 2013;8(3):e58161.
81. Yoshinari H et al. 110 Successful treatment of refractory lupus nephritis with secukinumab in a patient complicated with psoriasis vulgaris. Lupus Sci Med. 2017;4(Suppl 1):47-8.
82. Chun HY et al. Cytokine IL-6 and IL-10 as biomarkers in systemic lupus erythematosus. J Clin Immunol. 2007;27(5):461-6.
83. Ravirajan CT et al. Effect of neutralizing antibodies to IL-10 and C5 on the renal damage caused by a pathogenic human anti-dsDNA antibody. Rheumatology. 2004;43(4):442-7.
84. Yin Z et al. IL-10 regulates murine lupus. J Immunol. 2002 Aug;169(4):2148–55.
85. Kitagori K et al. Osteopontin in systemic lupus erythematosus. Nihon Rinsho Meneki Gakkai Kaishi. 2017;40(2):118-23. (In Japanese).
86. Lee YH, Song GG. Correlation between circulating osteopontin level in systemic lupus erythematosus and disease activity and associations between osteopontin polymorphisms and disease susceptibility: A meta-analysis. Lupus. 2016;26(2):132-8.
87. Behrendt N et al. The urokinase receptor. Fibrinolysis and proteolysis. 1998;12:191-204.
88. Balabanov R et al. Expression of urokinase plasminogen activator receptor on monocytes from patients with relapsing-remitting multiple sclerosis: effect of glatiramer acetate (copolymer 1). Clin Diagn Lab Immunol. 2001;8(6):1196-203.
89. Tomokuni A et al. Elevated soluble Fas/APO-1 (CD95) levels in silicosis patients without clinical symptoms of autoimmune diseases or malignant tumours. Clin Exp Immunol. 1997;110(2):303-9.
90. Jodo S et al. Serum levels of soluble Fas/APO-1 (CD95) and its molecular structure in patients with systemic lupus erythematosus (SLE) and other autoimmune diseases. Clin Exp Immunol. 1997;107(1):89-95.
91. Oon S et al. Systematic review, and meta-analysis of steroid-sparing effect, of biologic agents in randomized, placebo-controlled Phase 3 trials for systemic lupus erythematosus. Semin Arthritis Rheum. 2018. [Epub ahead of print].

Disease-Modifying Antirheumatic Diets: The New Treatment Modalities for Rheumatoid Arthritis

Authors: Shweta Khanna, Kumar Sagar Jaiswal, *Bhawna Gupta

Disease Biology Laboratory, School of Biotechnology, Kalinga Institute of Industrial Technology (KIIT), Bhubaneswar, India
*Correspondence to bhawna.gupta@kiitbiotech.ac.in

Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: Ms Khanna and Mr Jaiswal contributed equally to this manuscript.

Received: 28.03.18

Accepted: 31.05.18

Keywords: Disease management, disease-modifying diets, nutrients, rheumatoid arthritis (RA), vitamins.

Citation: EMJ Rheumatol. 2018;5[1]:93-99.

Abstract

Autoimmune responses need to be identified and managed promptly to avoid deleterious consequences. Autoimmune diseases, such as rheumatoid arthritis (RA), are debilitating and can lead to a compromised quality of life for patients. Autoimmune disease severity is directly related to sex (females are more prone to the diseases), as well as age, the environment, and genetic factors. Though many of these triggers cannot be avoided, disease onset and progression can be delayed, managed, and to some extent avoided altogether by dietary interventions. Certain food and dietary components have been observed to have anti-inflammatory properties and can thus be included in a patient's diet to reduce disease symptoms. This review will assess dietary components with regard to RA, including those that are frequently observed to be different in patients with RA in comparison to healthy individuals. The authors conclude that assessment of the nutritional status of a patient, including the deficiency of vitamins or other nutrients and energy requirements, should be recorded and a dietary regimen should be designed accordingly for a better therapeutic response.

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory, chronic, autoimmune disease leading to systemic inflammation and joint damage, making the patient compromised and dependent.[1] Prolonged pharmacological treatments often maintain patients in remission, reducing pain and joint damage;[2] however, continuous use of these drugs causes various side effects, including intestinal disorders, reduced calorie intake, and increased nutrient deficiency,[3] altering the nutritional profile of patients due to changes in ingestion, digestion, absorption, and excretion of food.[4] Such changes to a patient's nutritional profile are also observed during the natural course of RA;[3] therefore, it is important to supplement patients with nutrients and other dietary components to protect them from disease worsening.[3]

RA is known to be linked to genetic and environmental factors,[5] as well as nutritional imbalances.[6,7] Therefore, all of these factors must be considered for management of the disease, as well as when designing effective therapeutic regimens. In a previous review,[7]

the authors discussed various diets and food components that can help keep RA patients in remission, highlighting the need for an alternative pharmacological treatment to control the progression of disease.

Along with attention to diet and dietary compounds, the medical community needs to focus on various vitamins and minerals that are limited in patients with RA and understand their role in maintaining health. Meeting nutritional requirements using certain diets helps to lower pain and inflammation, inhibit the progression of disease, and boost the immune system. External supplementation of nutrients is one of the conventional approaches to meeting the nutritional requirements of the body, but this approach has been overcome by growing interest towards natural resources, such as food and dietary interventions. Based on the levels of nutritional deficiency, a dietician can suggest whether to administer external supplementation or to continue with natural resources. External supplementations are concentrated extracts and, in cases of severe deficiency, can be a suitable solution to manage disease, leaving natural resources to help diminish mild-to-moderate deficiencies. However, the nutrient bioavailability from dietary food sources depends on several external factors (food matrix and chemical form of nutrients) and internal or host factors (age, sex, nutritional profile, gastrointestinal effects, adhesion, and uptake by the intestinal mucosa). Depending on nutritional status, habitual diet, and several host factors, diet-based nutritional interventions may differ from patient to patient.

This review will discuss the nutritional statuses of RA patients and highlight the importance of nutritional assessment of these patients during disease progression for the effective treatment of the disease. Several roles and sources of dietary supplements are also summarised that will help clinicians and dieticians, as well as patients, in the effective management of the disease.

NUTRITIONAL INTERVENTION WITH FOOD COMPOUNDS

Alongside conventional disease-modifying antirheumatic drugs, aspirin and nonsteroidal anti-inflammatory drugs have been prescribed for inflammation and pain in RA. These drugs also induce some side effects that can hamper the immune system. For example, methotrexate treatment can lead to mouth sores (stomatitis), and patients taking disease-modifying antirheumatic drugs can experience abdominal pain, loss of appetite, nausea, and a sore tongue.[8] Thus, there is a need for medication with curative capabilities and without any side effects.

The potential of dietary intervention has always been a topic of discussion for the effective management of RA,[7] and several components have been tested and have proven to limit disease progression.[7] Although multiple reports have suggested nutritional imbalances in RA patients, as well as advised consumption of natural supplements, a comprehensive assessment of the nutritional value and bioavailability of supplements, so that they can be prescribed effectively, is lacking. This review will assess the role of different nutrients, minerals, food components, fruits, and vegetables, as well as the energy requirements of RA patients, for effective management of the disease.

Vitamins

Vitamin B6 is often found to be low in RA patients,[9] though this is not necessarily due to decreased intake or increased excretion.[9] Being inversely correlated with erythrocyte sedimentation rate (ESR), C-reactive protein level, disability score, pain, and morning stiffness in RA,[10] vitamin B6 supplementation did not improve RA markers or symptoms,[9] indicating deficiency to be a result of the inflammation. Moreover, proinflammatory cytokines (IL-6 and TNF-α) were suppressed with vitamin B6 at high doses.[11] Reduced physical activity increases the risk of cardiovascular diseases, which was significantly lowered upon vitamin B supplementation,[12] indicating that though vitamin B6 supplementation cannot directly suppress RA, it can effectively reduce risk factors of other opportunistic diseases. Thus, proper vitamin B6 supplementation in RA can help the body to manage the ongoing inflammation and prevent the occurrence of other diseases caused by its deficiency.[9]

Lower levels of vitamin D have been reported in RA patient blood serum and have a negative association with disease activity,[13] wherein its supplementation is known to improve disease

activity.[14] The vitamin is required by the body for calcium absorption and homeostasis, and a concomitant low calcium level is reported in RA patients.[15,16] In addition, vitamin D has an immunoregulatory role, aiding the effective functioning of immune cells;[17] therefore, vitamin D deficiency can aggravate RA.

Reactive oxygen species produced by immune cells are a major contributor to inflammation and joint damage in RA patients. Antioxidants protect against tissue damage due to reactive oxygen species by suppressing the production of cytokines and collagenase; RA patients have low levels of antioxidants, including vitamin C and E, β-carotene, zinc, selenium,[4] α-tocopherol,[15] vitamin A, and reduced activity of superoxide dismutase and glutathione peroxidase (GPx).[17] An inverse association has been found between RA disease activity and supplementation of vitamin C, E, β-cryptoxanthin, zinc, copper, manganese, fruits, and cruciferous vegetables,[4] suggesting that reduced levels of antioxidants may play a role in the progression of RA.[15] Thus, foods that are rich sources of various anti-inflammatory and antioxidant compounds have shown beneficial effects against chronic inflammatory diseases.[18]

Vitamin E, an important antioxidant, is often significantly decreased in RA patients, suggesting an increased possibility of oxidative damage.[17] A murine model of RA, when supplemented with oral vitamin E, did not show an improvement in disease status; however, the supplementation prevented joint destruction and led to significantly reduced IL-1β.[19] Patients supplemented with omega-3 and vitamin E showed significant reductions in malondialdehyde levels, but no effect on the activity of antioxidant enzymes or improvements in the clinical outcome of disease were observed.[20] Moreover, supplementation with 600 IU of vitamin E on alternate days did not contribute to a reduced risk of RA occurrence.[21] Therefore, although no direct effect of vitamin E supplementation on RA activity has been shown, it can protect against oxidative damage.

Minerals

Significant decreases in serum calcium and increases in serum phosphorous levels can lead to altered bone metabolism.[22] Reduced calcium levels may be the result of reduced absorption, an altered oxidative metabolism changing the intracellular ionic environment, or a side effect of glucocorticoid treatment, which reduces calcium absorption in the body.[23] Increased serum phosphorous is related to tissue hypoxia and increased degradation of ATP, leading to the release of inorganic phosphate into the blood circulation. Any alteration of the calcium:phosphorous ratio in patients will lead to altered bone metabolism;[22] therefore, maintaining a healthy level of these minerals in RA patients will help to reduce the disease progression and related damage, although more clinical studies are required. Moreover, supplementation of calcium should be undertaken, keeping in mind the risks, such as cardiovascular disease. Reduced serum or plasma levels of zinc,[24] magnesium,[25,26] potassium,[26] and selenium,[27] and increased levels of copper[24] and sodium[26] are observed in RA patients. Lower zinc and higher copper levels are known to correlate with active disease.[24] It was reported that increased IL-1 levels in patients can increase metallothionein levels, which may chelate circulating zinc;[28] moreover, zinc-containing proteins accumulate in the liver and in inflamed joints, leading to reduced plasma zinc levels in patients.[29] Patients supplemented with zinc sulphate showed improvements in laboratory and clinical parameters for RA.[30] Zinc is primarily involved in the efficient functioning of the immune system and is an important part of superoxide dismutase.[30] Zinc also inhibits the NF-κB pathway and decreases proinflammatory cytokine production,[17] as well as having a bone-forming effect and reducing osteoclast activity.[17] Thus, zinc deficiency may play an essential role in the inflammatory process of RA.

Increased levels of copper are present in the serum and hair of patients with RA, but the levels are significantly decreased in the erythrocytes.[31] Patients living in areas with high copper-containing farm soil have increased white blood cell counts, ESR, and Disease Activity Score 28 values, and blood levels of nickel and copper correlate positively with ESR.[32] Copper levels rise due to increased synthesis of ceruloplasmin by the liver,[29] and serum ceruloplasmin levels are also positively correlated with ESR.[31] In addition, serum magnesium and potassium levels decrease and negatively correlate with disease activity in RA patients,[25] while serum sodium levels are increased.[25]

However, there is limited experimental and clinical knowledge regarding sodium, potassium, and magnesium levels in relation to RA.

GPx activity is significantly reduced in RA patients and is controlled by levels of selenium. GPx controls intracellular reactive oxygen species levels by inhibiting the NF-κB pathway, leading to the production of inflammatory cytokines. Selenium levels are often low in RA patients and correlate negatively with disease activity;[33] a lack of selenium leads to reduced GPx activity, which may play a role in increasing inflammation and progression of RA. Selenium supplementation has been shown to increase blood selenium concentration, with subsequent increases in GPx activity in the serum and red blood cells, although selenium and GPx concentrations remained unchanged in polymorphonuclear cells, which might have resulted in a lack of clinical response in RA patients upon selenium supplementation.[34]

Iron is required by immune cells to function. Excessively elevated levels of iron can cause oxidative stress and increase the risk of infection, while altered iron homeostasis plays a role in autoimmune diseases, immune system dysregulation, and gout.[35] Significantly decreased serum iron concentration, total iron binding capacity, and haemoglobin levels are observed in RA patients,[36] and lower haemoglobin levels are related to greater disease activity.[37] Proinflammatory cytokines are known to affect iron metabolism, causing iron deficiency and anaemia in patients.[38] Anaemia of chronic disease (ACD) is the body's protective mechanism to reduce the available amount of free iron by converting it into ferritin during the course of inflammation or infection, thus leading to a decline in haemoglobin levels. On the other hand, a disease that causes blood loss can lead to the development of iron deficiency anaemia (IDA); thus, oral iron supplementation will be beneficial for patients with IDA but harmful for patients with ACD.[39] A higher number of RA patients have ACD compared to IDA, and ACD patients have a more severe disease with reduced recovery from anaemia upon iron supplementation when compared to IDA patients.[40] The type of anaemia a patient has must be carefully studied and then the deficiency supplemented to prevent disease worsening.

Calories

Contrary to the old adage 'if a little is good, more is better', it is important to assess the energy needs of RA patients compared to a healthy person to prevent obesity or becoming overweight. Differences in energy needs can be simply attributed to subtle differences in metabolism between RA patients and healthy people. Studies have reported that increased energy uptake leads to changes in disease activity.[41] It has been shown that resting energy expenditure in RA patients is 1% higher than in controls, but when fat-free mass is considered, the resting energy expenditure increases to 62 kcal/kg in RA patients, while for controls it is limited to up to 46 kcal/kg.[41] In addition, physical activity expenditure has been found to be 250 kcal lower in women with RA when compared with healthy controls. Since elevation in resting energy expenditure can be attributed to hypermetabolism, it may affect the total energy expenditure.[42,43] Therefore, an increase in energy uptake should not be advised for RA patients because it may lead to fat accumulation, resulting in obesity and hindering routine activities.[42,44] To minimise infection risk and maintain health, it is essential to preserve the fat-free mass, which can be achieved with the help of diet, exercise, and pharmacological interventions.[43]

Protein

The dietary reference intake suggests consuming approximately 1.0–1.6 g/kg of body weight of protein to prevent the loss of muscle mass.[45] Since there are no reports advising optimal protein intake for RA patients, dieticians can recommend optimal uptake for individual patients depending on their nutritional requirements.[43] No significant association between protein uptake and RA has been reported.[46]

Fats

Monounsaturated fats, like omega-3 or omega-6 fatty acids, directly benefit RA patients due to their immunosuppressive and anti-inflammatory activities. Consumption of omega-3 fatty acids can adjust the immune response, leading to improvements in symptoms like morning stiffness and tender joints; omega-3 fatty acid consumption is preferable over nonsteroidal

anti-inflammatory drugs or corticosteroids.[47,48] In addition, omega-6 fatty acid or gamma-linolenic acid intake as part of the patient's daily diet can decrease tender and swollen joint scores.[49] While recommending fat intake to a patient, monitoring the omega-6:omega-3 fatty acid ratio is important, since this ratio is comparatively higher in people who consume a Western diet and is generally considered proinflammatory.[50] Fish oils are known to harbour high amounts of omega-3 fatty acids and a daily consumption of approximately 3.6 g of omega-3 fatty acids has been shown to significantly reduce morning stiffness and increase grip strength in RA patients.[51] Ethyl ester derivatives of omega-3 fatty acids (e.g., eicosapentaenoic and docosahexaenoic acids) have the ability to reduce the symptoms of RA.[52]

Consumption of saturated fatty acids leads to a significant increase in biomarkers of inflammation, including C-reactive protein and IL-8; however, no specific recommendation about their intake is available for RA patients.[53,54] As a result, dieticians may recommend the standard levels of dietary fats to RA patients, keeping in mind cardiovascular disease and dyslipidaemia in lighter or low BMI patients.[55,56] Increased inflammation in RA is associated with significantly reduced levels of triglycerides, high-density lipoprotein cholesterol, and total cholesterol in the serum of patients, as well as significantly high levels of low-density lipoprotein cholesterol.[57] Patients with low reserves of fats have reduced vitamin A and E levels, which further increases lipid peroxidation and alters the lipid profile, causing significant muscle depletion and worsening of RA.[3]

Fruits and Vegetables

Fruits and vegetables are rich in phytochemicals and daily consumption can suppress inflammation and enhance antioxidant activity.[7] Polyphenols from dried plums are well known to inhibit TNF-α and nitric oxide synthase, and can stop the activity of transcription factor-nuclear factor for activated T cells.[58] Further, anthocyanins from rice and soybeans can reduce the levels of TNF-α and can suppress disease activity,[59] while resveratrol, a phytochemical from black grapes, can reduce markers of RA such as serum rheumatoid factor, cartilage oligomeric matrix protein, and matrix metalloproteinase-3; immunoglobulin G; proinflammatory cytokines (like TNF-α), and oxidative stress.[60] Mangiferin from mangoes and kaempferols and p-coumaric acid from grapefruits can positively reduce symptoms of RA by inhibiting several inflammatory pathways.[7]

CONCLUSION

Checking the nutritional status of RA patients is important for maintaining immunity and overall health. RA-related damage is inevitable and is aided by side effects of medication, leading to lower nutrition absorption or increased metabolism, thus reducing the quality of a patient's nutritional status. This inevitable damage caused by disease, both naturally and because of medications, can be delayed in RA patients by early assessment of nutritional status, helping prevent disease progression. The aforementioned observations suggest that nutrition is an important factor in RA and is involved in the progression and outcome of the disease. Despite the fact that nutrition and its impact on disease progression has received much attention, its role is not emphasised during the training of rheumatologists in medical schools; however, it can be argued that designing and suggesting a nutritional plan is the role of a dietician and not of a rheumatologist, although rheumatologists consult face-to-face with the patients and are often asked about dietary interventions. The authors therefore suggest that clinicians should be trained for basic awareness on the topic to aptly counsel their patients. One specific diet alone cannot provide all the necessary micronutrients, making it impossible to meet the exact nutritional requirements of the body, and therefore regular consumption of a variety of foods in sufficient amounts is of paramount importance to maintain nutritional balance. For example, cereals are the major source of iron and zinc, while fruits and vegetables may serve as the sole provider of vitamin C. Single and short-term interventions may not be sufficient to manage moderate and severe nutritional deficiencies, but a balanced combination of different interventions may be effective. A combination of interventions represents the perfect mix of micronutrients, different whole foods, and a complete diet potent enough to help the body acquire a nutritional equilibrium.

It can be inferred that RA patients must undergo initial body composition status check-ups to prevent harm from factors that can be easily negated. A patient's nutritional status can be determined using anthropometric (weight, height, tricep and bicep skinfold thickness, BMI, and arm circumference) and biochemical analyses (serum albumin, thyroxine-binding prealbumin, transferrin, folic acid, zinc, and retinol binding protein), as well as dietary intake measurements (food frequency questionnaire).[3,6] Strict control of a patient's nutritional status can be easily achieved by diet, and can help in the management of RA[7] and prevent occurrence of other associated diseases.[3] The authors thus suggest that the nutritional profile of the patient should be considered during treatment and the patient must be externally supplemented with deficient nutrients to minimise the side effects of medications and maintain wellbeing. Therefore, it is imperative for rheumatologists and dieticians to work in parallel to control the progression of RA by considering both physiological and nutritional requirements of their patients.[61]

References

1. Gibofsky A. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. Am J Manag Care. 2012;18(13 Suppl):S295-302.
2. Curtis JR, Singh JA. Use of biologics in rheumatoid arthritis: Current and emerging paradigms of care. Clinical therapeutics. 2011;33(6):679-707.
3. dos Santos AT et al. Assessment of nutritional and biochemical status in patients with rheumatoid arthritis undergoing pharmacological treatment. A pilot study. Int J Clin Exp Med. 2016;9(2):4282-90.
4. Cerhan JR et al. Antioxidant micronutrients and risk of rheumatoid arthritis in a cohort of older women. Am J Epidemiol. 2003;157(4):345-54.
5. Sparks JA, Costenbader KH. Genetics, environment, and gene-environment interactions in the development of systemic rheumatic diseases. Rheum Dis Clin North Am. 2014;40(4):637-57.
6. Helliwell M et al. Nutritional status in patients with rheumatoid arthritis. Ann Rheum Dis. 1984;43(3):386-90.
7. Khanna S et al. Managing rheumatoid arthritis with dietary interventions. Front Nutr. 2017;4:52.
8. Duncan K. Nutrition and Rheumatoid Arthritis. Available at http://www.todaysdietitian.com/pdf/courses/DuncanRheumatoidArthritis.pdf. Last accessed: 1 June 2018.
9. Chiang EP et al. Pyridoxine supplementation corrects vitamin B6 deficiency but does not improve inflammation in patients with rheumatoid arthritis. Arthritis Res Ther. 2005;7(6):R1404-11.
10. Chiang EP et al. Abnormal vitamin B 6 status is associated with severity of symptoms in patients with rheumatoid arthritis. Am J Med. 2003;114(4):283-7.
11. Huang SC et al. Vitamin B6 supplementation improves pro-inflammatory responses in patients with rheumatoid arthritis. Eur J Clin Nutr. 2010;64(9):1007-13.
12. Yxfeldt A et al. Homocysteine in patients with rheumatoid arthritis in relation to inflammation and B–vitamin treatment. Scand J Rheumatol. 2003;32(4):205-10.
13. Hajjaj-Hassouni N et al. Evaluation of vitamin d status in rheumatoid arthritis and its association with disease activity across 15 countries: "The COMORA study". Int J Rhumatol. 2017;2017:5491676.
14. Chandrashekara S, Patted A. Role of vitamin D supplementation in improving disease activity in rheumatoid arthritis: An exploratory study. Int J Rhum Dis. 2017;20(7):825-31.
15. Silva G et al. Micronutrients deficiencies in rheumatoid arthritis patients. Int J Pathol Clin Res. 2016;2(1):029.
16. Comstock GW et al. Serum concentrations of α tocopherol, β carotene, and retinol preceding the diagnosis of rheumatoid arthritis and systemic lupus erythematosus. Ann Rheum Dis. 1997;56(5):323-5.
17. Karatas F et al. Antioxidant status & lipid peroxidation in patients with rheumatoid arthritis. Indian J Med Res. 2003;118:178.
18. Al-Okbi SY. Nutraceuticals of anti-inflammatory activity as complementary therapy for rheumatoid arthritis. Toxicol Ind Health. 2014;30(8):738-49.
19. De Bandt M et al. Vitamin E uncouples joint destruction and clinical inflammation in a transgenic mouse model of rheumatoid arthritis. Arthritis Rheum. 2002;46(2):522-32.
20. Walwadkar S et al. Oxidative stress and calcium-phosphorus levels in rheumatoid arthritis. Indian J Clin Biochem. 2006;21(2):134-7.
21. Kolahi S et al. The evaluation of concurrent supplementation with vitamin E and omega-3 fatty acids on plasma lipid per oxidation and antioxidant levels in patients with rheumatoid arthritis. Internet J Rheumatol. 2011;7(1):1cf7.
22. Karlson EW et al. Vitamin E in the primary prevention of rheumatoid arthritis: The women's health study. Arthritis Rheum. 2008;59(11):1589-95.
23. Saptarini NM et al. Correlation study of serum calcium levels and serum cartilage oligomeric matrix protein levels in rheumatoid arthritis patients in bandung, Indonesia. Asia J Pharmaceut Clin Res. 2017;10(11):401.
24. Caglayan O, Aydog YS. Serum zinc and copper levels in rheumatoid arthritis. J Islamic Acad Sci. 1997;10(1):19-24.
25. Manole C et al. Changes of serum magnesium levels in patients with rheumatoid arthritis stage i-ii before treatment. Medical Connections. 2011;2(22):9-12. Available at: https://pdfs.semanticscholar.org/9174/7b393a085d6697816aef862b6b3531195255.pdf. Last accessed: 5 June 2018.
26. Alaly RA et al. The relation of serum sodium, potassium and magnesium with rheumatoid arthritis symptoms. Med J Babylon. 2012;9(4):912-7.
27. Yu N et al. The association between serum selenium levels with rheumatoid arthritis. Biol Trace Elem Res. 2016;172(1):46-52.
28. Wanchu A et al. Serum zinc levels in patients with active rheumatoid arthritis. J Indian Rheum Assoc. 1996;4(3):96-8.
29. Zoli A et al. Serum zinc and copper in active rheumatoid arthritis: Correlation with interleukin 1β and tumour necrosis factor α. Clin Rheumatol. 1998;17(5):378-82.

30. Al-Ali et al. Clinical evaluation of zinc therapy in rheumatoid arthritis. Med J Basrah Uni. 2007;25(2).

31. Strecker D et al. Copper levels in patients with rheumatoid arthritis. Ann Agric Environ Med. 2013;20(2):312-6.

32. Yang TH et al. Increased inflammation in rheumatoid arthritis patients living where farm soils contain high levels of copper. J Formos Med Assoc. 2016;115(11):991-6.

33. Tarp U et al. Selenium in rheumatoid arthritis. A historical prospective approach. J Trace Elem Electrolytes Health Disease. 1989;3(2):93-5.

34. Tarp U et al. Glutathione redox cycle enzymes and selenium in severe rheumatoid arthritis: Lack of antioxidative response to selenium supplementation in polymorphonuclear leucocytes. Ann Rheum Dis. 1992;51(9):1044-9.

35. Baker JF, Ghio AJ. Iron homoeostasis in rheumatic disease. Rheumatology. 2009;48(11):1339-44.

36. Dwivedi S et al. Levels of hemoglobin, ESR, iron & TIBC in rheumatoid arthritis patients compared with normal individuals. J Med Sci Clin Res. 2016;4(3).

37. Furst DE et al. Prevalence of low hemoglobin levels and associations with other disease parameters in rheumatoid arthritis patients: evidence from the CORRONA registry. Clin Exp Rheumatol. 2009;27(4):560-6.

38. Manel BHM et al. Hepatic proteins and inflammatory markers in rheumatoid arthritis patients. Iran J Public Health. 2017;46(8):1071.

39. Iron Disorder Institute. Anemia of Chronic Disease. 2009. Available from: http://www.irondisorders.org/anemia-of-chronic-disease. Last accessed: 1 June 2018.

40. Peeters H et al. Course and characteristics of anaemia in patients with rheumatoid arthritis of recent onset. Ann Rheum Dis. 1996;55(3):162-8.

41. Guo S et al. Alterations and diagnosis potential of serum lipid profiles in rheumatoid arthritis patients. Int J Clin Exp Pathol. 2017;10(3):3503-9.

42. Binymin K et al. The effect of disease activity on body composition and resting energy expenditure in patients with rheumatoid arthritis. J Inflamm Res. 2011;4:61-6.

43. Roubenoff R et al. Low physical activity reduces total energy expenditure in women with rheumatoid arthritis: Implications for dietary intake recommendations. Am J Clin Nutr. 2002;76(4):774-9.

44. Rall L, Roubenoff R. Rheumatoid cachexia: Metabolic abnormalities, mechanisms and interventions. Rheumatology. 2004;43(10):1219-23.

45. Ajeganova S et al. Association of obesity with worse disease severity in rheumatoid arthritis as well as with comorbidities: A long–term followup from disease onset. Arthritis care Res. 2013;65(1):78-87.

46. Bernstein M, Munoz N. Position of the academy of nutrition and dietetics: Food and nutrition for older adults: Promoting health and wellness. J Acad Nutr Diet. 2012;112(8):1255-77.

47. Benito-Garcia E et al. Protein, iron, and meat consumption and risk for rheumatoid arthritis: A prospective cohort study. Arthritis Res Therapy. 2007;9(1):R16.

48. Miles EA, Calder PC. Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis. Br J Nutr. 2012;107(S2):S171-84.

49. Stamp LK et al. Diet and rheumatoid arthritis: A review of the literature. Semin Arthritis Rheum. 2005;35(2):77-94.

50. Leventhal LJ et al. Treatment of rheumatoid arthritis with gammalinolenic acid. Ann Intern Med. 1993;119(9):867-73.

51. Patterson E et al. Health implications of high dietary omega-6 polyunsaturated fatty acids. J Nutr Med. 2012;2012:539426.

52. Nielsen G et al. The effects of dietary supplementation with n–3 polyunsaturated fatty acids in patients with rheumatoid arthritis: A randomized, double blind trial. Eur J Clinical Invest. 1992;22(10):687-91.

53. Kremer JM et al. Effects of high–dose fish oil on rheumatoid arthritis after stopping nonsteroidal antiinflammatory drugs clinical and immune correlates. Arthritis Rheum. 1995;38(8):1107-14.

54. Kantor ED et al. Lifestyle factors and inflammation: Associations by body mass index. PLoS One. 2013;8(7):e67833.

55. Muñoz A, Costa M. Nutritionally mediated oxidative stress and inflammation. Oxid Med Cell Longev. 2013;2013:610950.

56. Singh HV et al. Atherogenic lipid profile and high sensitive C-reactive protein in patients with rheumatoid arthritis. Clin Biochem. 2013;46(12):1007-12.

57. Kremers HM et al. Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis. Arthritis Rheum. 2004;50(11):3450-7.

58. Bu SY et al. Dried plum polyphenols inhibit osteoclastogenesis by downregulating NFATc1 and inflammatory mediators. Calcified tissue international. 2008;82(6):475-88.

59. He YH et al. Anti–inflammatory and anti–oxidative effects of cherries on Freund's adjuvant–induced arthritis in rats. Scand J Rheumatol. 2009;35(5):356-8.

60. Wahba MG et al. Protective effects of fenofibrate and resveratrol in an aggressive model of rheumatoid arthritis in rats. Pharm Biol. 2016;54(9):1705-15.

61. Schieszer J. Correcting nutritional alterations in patients with rheumatologic disease to improve quality of life. 2016. Available from: https://www.rheumatologyadvisor.com/rheumatoid-arthritis/correcting-nutritional-alterations-in-patients-with-ra/article/506932/. Last accessed: 1 June 2018.

Stroke and Systemic Lupus Erythematosus: A Review

Authors: Marco Cavallaro, Ugo Barbaro, Antonio Caragliano, Marcello Longo, Giuseppe Cicero, Francesca Granata, *Sergio Racchiusa

Department of Biomedical Sciences and Morphological and Functional Imaging, University of Messina, Policlinico "G. Martino", Messina, Italy
*Correspondence to sergioracchiusa@gmail.com

Disclosure: The authors have declared no conflicts of interest.

Received: 15.03.18

Accepted: 04.06.18

Keywords: Endothelium, inflammation, intracerebral haemorrhage (IH), stroke, subarachnoid haemorrhage (SAH), systemic lupus erythematosus (SLE).

Citation: EMJ Rheumatol. 2018;5[1]:100-107.

Abstract

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that involves collagen tissue throughout the body. Several previous studies have shown that the risk of ischaemic and haemorrhagic stroke is significantly higher in SLE when compared to the general population, particularly in young individuals, representing one of the principal causes of death in these patients. Though the precise pathophysiology behind this increased risk is still poorly understood, several mechanisms are suggested to play a role. The high burden of cerebral small vessel disease features noted on brain neuroimaging studies, as well as the accelerated process of atherosclerosis identified in these patients, are likely to be responsible for at least some of the ischaemic strokes occurring in the SLE population. Repeated episodes of arterial and venous thrombosis secondary to antiphospholipid syndrome are likewise important. Less is known regarding the exact pathophysiological relationship between SLE and the high incidence of haemorrhagic stroke, though thrombocytopenia and a greater susceptibility to form typical and atypical brain aneurysms, which may then rupture, are thought to be the main mechanisms responsible for the occurrence of intracerebral and subarachnoid haemorrhage, respectively. Both inflammatory and noninflammatory events, all involving the immune system, are responsible for several pathological changes affecting cerebral vessels of every calibre in SLE, as confirmed by histopathology. In this context, endothelial activation and dysfunction play a critical role. This review will briefly analyse the most important factors responsible for the higher ischaemic and haemorrhagic stroke risk in the SLE population, with a particular focus on brain vascular changes.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that causes inflammation in connective tissues throughout the body. Prevalence ranges from a few to 241 cases per 100,000 people, with women and people of black ethnicity being more frequently affected.[1] Numerous studies have shown that individuals with SLE have a higher risk of cerebrovascular events than the general population.[2,3] Stroke and cerebrovascular events in general are among the main specific causes of death in SLE patients, representing 10–15% of all deaths in this population.[4]

Box 1: Principal factors implicated in the higher stroke incidence in systemic lupus erythematosus patients.

Ischaemic stroke

- Higher burden of cerebral small vessel disease.
- Accelerated atherosclerosis.
- Antiphospholipid syndrome and arterial and venous thrombosis.
- Cerebral vasculitis.
- Vessel dissection.
- Other minor factors (e.g., cardiogenic thromboemboli in Libman–Sacks disease; infections).

Haemorrhagic stroke

- Intracerebral haemorrhage
  - Thrombocytopenia.
  - Anticoagulants.
  - Secondary hypertension.
  - Cerebral vasculitis.
  - Other factors (haemorrhagic transformation of ischaemic infarction; other disorders of blood coagulation).
- Subarachnoid haemorrhage
  - Typical aneurysm rupture (saccular or 'belly' aneurysm).
  - Atypical aneurysm rupture (distal fusiform aneurysms, multiple aneurysms with atypical locations).
  - 'Angiogram-negative' subarachnoid haemorrhage.

It has been demonstrated that in patients with SLE, the risk of any kind of stroke, ischaemic or haemorrhagic, is higher when compared to the general population, particularly in patients <50 years old.[2,5,6] Specifically, studies have reported a 2-fold increased risk for ischaemic stroke and 2–3-times greater risk for intracerebral haemorrhage (IH) in SLE patients in comparison with the general population.[2,5] Moreover, apart from overt neurological syndromes, silent vascular damage, evaluated with MRI, is augmented in SLE.[5] Subarachnoid haemorrhage (SAH) also seems more frequent in SLE patients compared to the general population, with a reported incidence rate of 49.4 versus 10.2 per 100,000 person-years.[7] Although the exact mechanisms responsible for the increased stroke risk in SLE are not yet fully understood, numerous hypotheses have been formulated. The aim of this review is to analyse the different factors contributing to the higher risk of stroke in the SLE population, with a focus on cerebral vascular changes (Box 1).

CEREBRAL VASCULAR CHANGES IN SYSTEMIC LUPUS ERYTHEMATOSUS AND THE ROLE OF ENDOTHELIUM

It is widely known that vascular involvement in SLE is a key factor for the development of numerous central nervous system pathological manifestations.[8] Both inflammatory and noninflammatory events affect cerebral vessels of every calibre. As further described below, all cerebral vessels, from large arteries to small vessels to veins, can potentially be involved in SLE.

Such a diffused vascular participation has been confirmed by numerous pathological studies reporting several changes affecting brain vessels, ranging from thrombosis, perivascular infiltration of inflammatory cells, and destructive and proliferative changes, comprising fibrinoid degeneration and endothelial cell proliferation.[9,10]

All of these mechanisms involve the immune system with different events: immune complex/complement injury, vasculopathy due to antiphospholipid (aPL) antibodies or dysfunctional platelets, plasma factors, endothelial cell adhesion molecules, and overt clotting due to aPL antibodies resulting in thrombosis or cardiac emboli to the brain.[11]

It would appear that the key factor in the pathogenesis of all of these events is endothelial cell damage and/or activation.[8,12,13] It is known that one of the main mechanisms involved is the direct binding of autoantibodies to certain molecules expressed on the surface of endothelial cells, such as beta 2 glycoprotein I,

which is considered to be among the most important.[12] This process, together with immune complex depositions, increases complement-dependent cytotoxicity and endothelial permeability and leads endothelial cells to express adhesion molecules, which attract circulating lymphocytes and monocytes. Atehortúa et al.[14] have also hypothesised a possible interaction of different monocyte subpopulations with endothelial cells, favouring alterations in the macro and microvascular context of SLE. The combination of these processes leads to prothrombotic activity induction, leukocyte subendothelial infiltration, and detachment of endothelial cells; for example, an increased number of circulating endothelial cells have been found in the blood of patients with SLE.[15] A peculiar susceptibility of the brain endothelium to these inflammatory mediators in comparison with endothelial cells from other anatomical regions has also been hypothesised.[12]

ISCHAEMIC STROKE

Cerebral Small Vessel Disease

One of the hypotheses for the higher stroke incidence in SLE patients is related to the association between SLE and cerebral small vessel disease (CSVD).

The term CSVD refers to various pathological processes affecting the perforating cerebral arterioles, capillaries, and venules of the brain, with subsequent parenchymal damage, mainly in the white matter and in the subcortical grey matter.[16] CSVD is very common, accounts for approximately 20% of all strokes, and increases the risk of future strokes by >50%;[17] symptoms include cognitive and balance impairment and dementia. Neuroimaging, particularly MRI, is essential for the diagnosis of CSVD, and some scores based on MRI features, such as lacunes, white matter hyperintensities, cerebral microbleeds, and enlarged perivascular spaces, have been developed to calculate a total CSVD burden, thus providing a standardised language and a baseline stratification of patients with CSVD.[18] Using MRI features, Wiseman et al.[19] showed that patients with SLE have a high burden of CSVD; MRI-dependent CSVD score was higher in SLE patients when compared to both healthy control patients and patients with minor stroke, despite the latter presenting more traditional cardiovascular risk factors.

Although the correlation between SLE and CSVD is not yet fully understood, it is hypothesised that inflammation, as it is the underlying factor in SLE, might well play an important role in the pathogenesis of CSVD. Pathological studies have showed inflammatory infiltrates in the perforating arteriolar walls,[20] and some authors have reported an association between the levels of C-reactive protein (CRP) and CSVD-related lesions.[21] Moreover, enlarged perivascular spaces, the MRI feature mainly responsible for the higher CSVD score in SLE patients,[19] have been shown to be associated with increased plasma markers of inflammation,[22] as well as with other inflammatory brain disorders such as multiple sclerosis.[23] Therefore, it is likely that some endothelial damage risk factors occurring in SLE, such as complement activation and immune complex deposition, could stimulate cerebrovascular inflammation, causing a high burden of CSVD, and are responsible for at least some of the ischaemic strokes in SLE patients.[19]

Accelerated Atherosclerosis

Numerous studies have identified an accelerated, premature process of atherosclerosis as one of the leading causes of the elevated risk of ischaemic stroke and cardiovascular events in patients with SLE.[24-28] Various hypotheses have been formulated to explain this phenomenon. Firstly, an increased prevalence of several traditional risk factors for atherosclerosis have been shown in the SLE population. Hypertension in particular has been found to be the most important traditional factor associated with SLE.[27] Diabetes also seems to be more common in SLE patients than the general population.[6,26] Furthermore, these patients are more likely to have a more sedentary lifestyle, higher very low-density lipoprotein-cholesterol and triglycerides, and lower high-density lipoprotein.[24,26]

However, traditional risk factors alone fail to explain the excess risk of atherosclerosis in SLE patients,[29] especially when the trend for higher stroke risk in people <50 years old is considered. A further confirmation also comes from some studies that found SLE to be associated with a high burden of early

atherosclerosis even after adjustment for classic risk factors was made.[28,30] Therefore, other SLE-related factors must be considered to explain the high atherosclerotic burden in these patients. Once again, systemic inflammation seems to play a pivotal role in the atherogenic process. It is known that inflammation is involved in all stages of atherogenesis, from the formation and evolution of atheroma to the thrombotic complications of this disease.[31] CRP has been demonstrated to be an active mediator in the pathogenesis of atherosclerosis,[31] and elevated levels of CRP have been found during the course of SLE, even in patients with inactive disease,[27] thus representing another factor involved in the accelerated atherosclerosis in SLE. SLE-related inflammation also contributes to several dyslipidaemic alterations associated with the development of atherosclerotic disease, such as hypercholesterolaemia, hypertriglyceridaemia, and the reduction in activity of lipoprotein lipase and other antioxidant enzymes.[26]

Autoimmune phenomena also play an important role in the atherogenic process. SLE-circulating immune complexes have been shown to stimulate the accumulation of cholesterol in cultured smooth muscle cells.[32] SLE autoantibodies, such as double strand-DNA autoantibodies and, when present, aPL antibodies, stimulate endothelial activation, which is considered one of the main and earliest steps in the atherogenic process. Enhanced endothelial activation is also demonstrated by the increased serum levels of some markers, such as vascular cell adhesion molecule-1 (VCAM-1), thrombomodulin, and von Willebrand factor, which have been shown to be augmented in SLE patients, even with inactive disease.[27]

Another important element in the development of atherosclerosis in the SLE population is an altered vascular remodelling, as proven by the elevated levels of some metalloproteinases, like MMP-3, found in the serum of these patients, and this increased activity has been demonstrated during many steps of atherosclerosis.[27,33] Several studies have shown that disease duration and damage index are also directly related to atherosclerosis.[25,28,29]

Conversely, the role of treatment, especially steroids, has not yet been fully established. Most authors have reported a direct correlation between elevated exposure to corticosteroids and the process of atherosclerosis.[26,34] Roman et al.,[28] on the other hand, found that SLE patients with carotid plaque presented lower average dose of prednisone than SLE patients without plaque. Antimalarials, in contrast, have generally been considered to have a beneficial anti-inflammatory and antiplatelet effect and have been associated with lower total cholesterol and triglyceride levels.[26,35] Other nontraditional factors, such as chronic renal impairment and homocysteine levels, have also been related to the accelerated atherogenesis occurring in SLE.[24,27]

Antiphospholipid Syndrome and Thrombosis

It has been noted that 25–40% of SLE patients have secondary aPL syndrome (APS), characterised by the presence of aPL antibodies with clinical features of repeated episodes of arterial or venous thrombosis, recurrent spontaneous abortions, or thrombocytopenia.[36] APS is a disorder characterised by thrombosis, which can be either venous, arterial, or both, and pregnancy loss in conjunction with the presence of lupus anticoagulant, or IgG or IgM anticardiolipin, or IgG or IgM anti-β_2-glycoprotein I.[37] The syndrome can be primary, when it occurs in the absence of any other related disease, or secondary, when it is associated with other autoimmune diseases, especially SLE (APS/SLE).[36]

In 2014, Kaichi et al.[38] retrospectively examined 256 SLE patients (45 with APS, 211 without APS) who had undergone MRI studies. They found a higher incidence of cerebral lesions in patients with APS/SLE. Large territorial infarctions, lacunar infarctions in the deep white matter, localised cortical infarctions in the middle cerebral artery (MCA) territory, bilateral border zone infarctions, anterior basal ganglia, and stenotic arterial lesions were found to be more common in SLE patients with APS than in those without.[38] The main factor responsible for vascular damage in APS/SLE is thought to be arterial and/or venous thrombosis. Arterial damage could be divided into large-artery occlusions (most commonly MCA) or into multifocal arterial stenoses. Focal regions of arterial narrowing have been noted within

branches of the anterior, middle, and posterior cerebral arteries.[39]

Venous occlusive disease has also been described in the intracranial circulation;[40] occlusion of dural venous sinuses and deep cerebral veins was reported with a prevalence of 29% in patients with APS.[41]

aPL antibodies are a heterogeneous family of antibodies that react against several anionic phospholipid-binding plasma proteins.[12] The presence of this family of autoantibodies in the serum, operating through cofactors (β_2-glycoprotein I or prothrombin), can generate a thrombotic diathesis. Although the mechanism for this hypercoagulable state is not yet fully understood, it appears to involve interactions between the antibodies to anionic phospholipid-protein complex and antigen targets on platelets, endothelial cells, or components of the coagulation cascade.[42]

Therefore, APS is likely to represent a key factor in the origin of ischaemic and venous stroke in SLE patients, as also reported by Valdés-Ferrer et al.,[43] who described a higher prevalence of strokes and leukoaraiosis in patients with APS/SLE than in those patients with only SLE.

Vasculitis

A true cerebral vasculitis in SLE is rare, with a reported incidence in pathological studies of <10%.[44] Clinical manifestations are highly variable, due to the potential of the inflammatory process to affect vessels of different sizes, and can range from mild cognitive impairment to severe neurological manifestations, including stroke, both ischaemic and haemorrhagic.[12] The involvement of large vessels is extremely rare and has been associated with the most serious neurological manifestations and extremely high mortality rates.[45,46]

The main pathophysiological processes implied are the *in situ* formation or the deposition of immune complexes within the vessel wall and the action of antibodies against endothelial cells.[13] Specifically, it has been shown that autoantibody binding to brain endothelial cell antigens can induce an endothelial activation eventually responsible for the vasculitic process.[12]

Other forms of SLE-related vasculitis can be drug-induced or infection-related, in the latter case either through direct damage of the vascular wall by micro-organisms or through antigen-induced autoimmune processes.[13]

Dissection

Arterial dissection is considered a very rare cause of ischaemic stroke; indeed, it has been reported that internal carotid artery dissection is responsible for <2% of all ischaemic strokes.[47,48] Similar to other connective tissue diseases, SLE has a higher risk of vascular dissection. The pathophysiological correlation between SLE and arterial dissection is not clearly known. Many factors may play a role and can co-operate,[49] determining a self-sustaining loop. Numerous factors are involved in the activation of autoinflammatory degeneration of vessel walls, such as endothelial and extracellular matrix damage, immune complex formation, and deposition.[5,50]

The chronic use of steroids induces arterial weakening and, along with hypertension, dyslipidaemia, and increased arterial stiffness, can lead to arterial wall dissection.

Despite the infrequent occurrence, when considering the possible aetiology of a SLE patient presenting with ischaemic stroke, the possibility of arterial dissection should be considered. Conversely, in a young patient presenting with stroke due to arterial dissection of unknown origin, it is mandatory to investigate a contingent coexistence of a rheumatic disease, such as SLE.[51]

HAEMORRHAGIC STROKE

Intracerebral Haemorrhage

IH in the SLE population is rarely reported in the literature.[2,6,52,53] It has been shown that, compared to the general population, SLE patients present a 2–3-fold higher risk of IH, especially at younger ages.[2,5,52]

Several factors, most of which are also associated with ischaemic stroke, are implicated in the pathogenesis of IH in SLE. One of the most important is considered to be thrombocytopenia, diagnosed in >50% of affected patients, which can be secondary to

different mechanisms, such as the administration of immunosuppressive agents, the presence of aPL antibodies, thrombotic microangiopathy, and bone marrow depression.[54,55]

Another important factor contributing to the high risk of IH in the SLE population is represented by the frequent use of anticoagulants to prevent thromboembolism events. This could also represent one of the reasons for the observation some authors have made that the longer the time from SLE diagnosis, the higher the relative risk of IH.[6]

The high prevalence of hypertension in the SLE population is another factor that is highly associated with a possible diagnosis of IH in these patients.[27] Furthermore, vessel wall weakness, due to endothelial dysfunction or to a concurrent true vasculitic process, may be responsible for a major propensity of the vessel to rupture, thus causing IH.[2,52] Eventually, the possibility of haemorrhagic transformation of an ischaemic infarction, especially after thrombolytic therapy, must also be considered.[56]

An interesting element confirming the more complex pathogenesis of IH in SLE patients in comparison with IH in the general population is the different anatomical localisation of the haemorrhages in the brain, which are often located in the cerebral lobes in the former group compared to the basal ganglia and internal capsule in the latter cases.[52,57]

Subarachnoid Haemorrhage

Several studies have showed a relatively frequent occurrence of SAH in SLE patients, with some authors reporting an up to 4-fold higher risk ratio and incidence rate compared to the general population.[2,7]

The causes of this increased incidence of SAH in SLE patients are not yet fully understood. Similar to the general population, rupture of intracranial aneurysms appears to be the most frequent cause of SAH in SLE patients.[7] However, most of these aneurysms often present peculiar features; apart from the classic saccular (or 'belly') aneurysms, as in the general population, uncommon lesions, like distal fusiform aneurysms and multiple little aneurysms with atypical locations, are often described when SAH occurs in SLE patients.[58] Furthermore, in some cases, SAH is not related to an obvious pathology, with no aneurysms or other pathological findings detected in the angiographic exams performed after SAH has occurred (the so called 'angiogram-negative SAH').[58,59]

Several pathophysiological hypotheses have been formulated to explain the higher incidence and the peculiar features of SAH in the SLE population. Once again, the increased prevalence of several traditional risk factors for SAH, especially hypertension and atherosclerosis, as well as endothelial damage, fibrinoid necrosis, and the activity index, represent key pathogenic factors for the onset of SAH, particularly for the greater likelihood of formation and rupture of classic saccular aneurysms.[58,60]

Cerebral vasculitis plays an important role too, especially in the genesis of atypical aneurysms; arterial inflammation causes lumen vessel narrowing and cerebral flow reduction, leading to ischaemia and haemodynamic stress, which are cofactors for aneurysmal genesis.[7,61] Very little is known regarding the pathogenesis of angiogram-negative SAH. Treatment-related complications, especially for corticosteroid therapy, are likely to be involved in many of these cases.[58,60] In fact, the use of a high daily dose of steroids has been shown to be an independent risk factor for an increased incidence of SAH.[7,58]

CONCLUSION

The risk of any stroke, whether ischaemic or haemorrhagic, is higher in SLE than the general population, especially in young individuals. Several traditional, potentially manageable risk factors, classically implicated in the genesis of stroke in the general population, play a critical role in the SLE population; for some of these risk factors, an increased prevalence has been noted in SLE patients compared to the general population. More attention and control of these factors (such as hypertension, diabetes, and anticoagulant dosage) are mandatory. However, classical risk factors alone fail to explain the higher incidence of stroke in SLE patients compared to the general population, especially when some elements are considered: the high incidence of stroke in people <50 years old,

the higher CSVD score compared to patients with a previously occurring minor stroke, the high burden of atherosclerosis even after adjustment for traditional risk factors, the occurrence of atypical or rare events (e.g., dissection and atypical aneurysms). Although the precise pathophysiology responsible is not completely understood, several mechanisms have been hypothesised; in this context, inflammation and endothelial cell activation and damage play a crucial role.

Considering the high mortality and morbidity related to stroke and the young age of people involved, future studies focussing on the correlation between stroke and SLE are highly recommended, hopefully providing new insights into the treatment and prevention of vascular brain damage in these patients.

References

1. Rees F et al. The worldwide incidence and prevalence of systemic lupus erythematosus: A systematic review of epidemiological studies. Rheumatology (Oxford). 2017;56(11):1945-61.
2. Holmqvist M et al. Stroke in systemic lupus erythematosus: A meta-analysis of population-based cohort studies. RMD Open. 2015;1(1):e000168.
3. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart. 2014;100(Suppl 2): ii1-67.
4. Cervera R et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: A comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore). 2003;82(5):299-308.
5. Wiseman SJ et al. Cerebrovascular disease in rheumatic diseases: A systematic review and meta-analysis. Stroke. 2016;47(4):943-50.
6. Arkema EV et al. Stroke in systemic lupus erythematosus: A Swedish population-based cohort study. Ann Rheum Dis. 2017;76(9):1544-9.
7. Chang YS et al. Increased risk of subarachnoid hemorrhage in patients with systemic lupus erythematosus: A nationwide population-based study. Arthritis Care Res (Hoboken). 2013;65(4):601-6.
8. Tsokos GC. Systemic lupus erythematosus. N Engl J Med. 2011;365(22):2110-21.
9. Funata N. Cerebral vascular changes in systemic lupus erythematosus. Bull Tokyo Med Dent Univ. 1979;26(2):91-112.
10. Graham EM et al. Cerebral and retinal vascular changes in systemic lupus erythematosus. Ophthalmology. 1985;92(3):444-8.
11. West S, "Systemic lupus erythematosus and the nervous system," Wallace DJ, Hahn BH (eds.), Dubois' lupus erythematosus (2006) 6th edition, Philadelphia: Williams and Wilkins, pp.707-36.
12. Meroni PL et al. Endothelium and the brain in CNS lupus. Lupus. 2003;12(12):919-28.
13. Radic M et al. Vascular manifestations of systemic lupus erythematosus. Neth J Med. 2013;71(1):10-6.
14. Atehortúa L et al. Endothelial alterations in systemic lupus erythematosus and rheumatoid arthritis: Potential effect of monocyte interaction. Mediators Inflamm. 2017;2017:9680729.
15. Rajagopalan S et al. Endothelial cell apoptosis in systemic lupus erythematosus: A common pathway for abnormal vascular function and thrombosis propensity. Blood. 2004;103(10):3677-83.
16. Pantoni L. Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010;9(7):689-701.
17. Wardlaw JM et al. Mechanisms of sporadic cerebral small vessel disease: Insights from neuroimaging. Lancet Neurol. 2013;12(5):483-97.
18. Staals J et al. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. Neurology. 2014;83(14):1228-34.
19. Wiseman SJ et al. Cerebral small vessel disease burden is increased in systemic lupus erythematosus. Stroke. 2016;47(11):2722-8.
20. Bailey EL et al. Pathology of lacunar ischemic stroke in humans - A systematic review. Brain Pathol. 2012;22(5):583-91.
21. Mitaki S et al. C-reactive protein levels are associated with cerebral small vessel-related lesions. Acta Neurol Scand. 2016;133(1):68-74.
22. Aribisala BS et al. Circulating inflammatory markers are associated with magnetic resonance imaging-visible perivascular spaces but not directly with white matter hyperintensities. Stroke. 2014;45(2):605-7.
23. Potter GM et al. Enlarged perivascular spaces and cerebral small vessel disease. Int J Stroke. 2015;10(3): 376-81.
24. Fors Nieves CE, Izmirly PM. Mortality in systemic lupus erythematosus: An updated review. Curr Rheumatol Rep. 2016;18(4):21.
25. Jiménez S et al. Preclinical vascular disease in systemic lupus erythematosus and primary antiphospholipid syndrome. Rheumatology (Oxford). 2005;44(6):756-61.
26. Bruce IN. Atherogenesis and autoimmune disease: The model of lupus. Lupus. 2005;14(9):687-90.
27. De Leeuw K et al. Traditional and non-traditional risk factors contribute to the development of accelerated atherosclerosis in patients with systemic lupus erythematosus. Lupus. 2006;15(10):675-82.
28. Roman MJ et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. N Engl J Med. 2003;349(25):2399-406.
29. Esdaile JM et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum. 2001;44(10):2331-7.
30. El-Magadmi M et al. Systemic lupus erythematosus: An independent risk factor for endothelial dysfunction in women. Circulation. 2004;110(4): 399-404.
31. Libby P et al. Inflammation and atherosclerosis. Circulation. 2002;105(9):1135-43.
32. Kabakov AE et al. The atherogenic effect of lupus sera: Systemic lupus erythematosus-derived immune complexes stimulate the accumulation of cholesterol

in cultured smooth muscle cells from human aorta. Clin Immunol Immunopathol. 1992;63(3):214-20.

33. Faber-Elmann A et al. Activity of matrix metalloproteinase-9 is elevated in sera of patients with systemic lupus erythematosus. Clin Exp Immunol. 2002;127(2):393-8.
34. Petri M et al. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. Am J Med. 1992;93(5):513-9.
35. Wallace DJ et al. Cholesterol-lowering effect of hydroxychloroquine in patients with rheumatic disease: Reversal of deleterious effects of steroids on lipids. Am J Med. 1990;89:322-6.
36. Danowski A et al. Determinants of risk for venous and arterial thrombosis in primary antiphospholipid syndrome and in antiphospholipid syndrome with systemic lupus erythematosus. J Rheumatol. 2009;36(6):1195-9.
37. Levine JS et al. The antiphospholipid syndrome. N Engl J Med. 2002;346(10):752-63.
38. Kaichi Y et al. Brain MR findings in patients with systemic lupus erythematosus with and without antiphospholipid antibody syndrome. AJNR Am J Neuroradiol. 2014;35(1):100-5.
39. Provenzale JM et al. Antiphospholipid antibodies in patients without systemic lupus erythematosus: Neuroradiologic findings. Radiology. 1994;192(2):531-7.
40. Bacharach JM et al. Imaging spectrum of thrombo-occlusive vascular disease associated with antiphospholipid antibodies. Radiographics. 1993;13(2):417-23.
41. Lalani TA et al. Imaging findings in systemic lupus erythematosus. Radiographics. 2004;24(4):1069-86.
42. Belmont HM et al. Pathology and pathogenesis of vascular injury in systemic lupus erythematosus. Interactions of inflammatory cells and activated endothelium. Arthritis Rheum. 1996;39(1):9-22.
43. Valdés-Ferrer SI et al. Cerebral changes in SLE with or without antiphospholipid syndrome. A case-control MRI study. J Neuroimaging. 2008;18(1):62-5.
44. Rowshani AT et al. Cerebral vasculitis as a primary manifestation of systemic lupus erythematosus. Ann Rheum Dis. 2005;64(5):784-6.
45. Böckle BC et al. Cerebral large vessel vasculitis in systemic lupus erythematosus. Lupus. 2014;23(13):1417-21.
46. Weiner DK, Allen NB. Large vessel vasculitis of the central nervous system in systemic lupus erythematosus: Report and review of the literature. J Rheumatol. 1991;18(5):748-51.
47. Majeed A et al. A rare presentation of spontaneous internal carotid artery dissection with Horner's syndrome, VIIth, Xth and XIIth nerve palsies. Oxf Med Case Reports. 2016;2016(10):omw078.
48. Kurre W et al. Endovascular treatment of acute internal carotid artery dissections: Technical considerations, clinical and angiographic outcome. Neuroradiology. 2016;58(12):1167-79.
49. Wei HY et al. Aortic dissection complicated with hemothorax in an adolescent patient with systemic lupus erythematosus: Case report and review of literature. Semin Arthritis Rheum. 2011;41(1):12-8.
50. Pyrpasopoulou A et al. Vascular disease in systemic lupus erythematosus. Autoimmune Dis. 2012;2012:876456.
51. Racchiusa S et al. Endovascular treatment of spontaneous intracranial internal carotid dissection in a young patient affected by systemic lupus erythematosus: A case report. J Vasc Interv Neurol. 2017;9(5):1-7.
52. Gao N et al. Clinical characteristics and risk factors of intracranial hemorrhage in systemic lupus erythematosus. Lupus. 2013;22(5):453-60.
53. Zöller B et al. Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: A nationwide follow-up study from Sweden. BMC Neurol. 2012;12:41.
54. Bernatsky S et al. Mortality related to cerebrovascular disease in systemic lupus erythematosus. Lupus. 2006;15(12):835-9.
55. Cines DB et al. Pathobiology of secondary immune thrombocytopenia. Semin Hematol. 2009;46(1 Suppl 2):S2-14.
56. Zhang J et al. Hemorrhagic transformation after cerebral infarction: Current concepts and challenges. Ann Transl Med. 2014;2(8):81.
57. Aguilar MI, Brott TG. Update in intracerebral hemorrhage. Neurohospitalist. 2011;1(3):148-59.
58. Torné R et al. Subarachnoid hemorrhage in systemic lupus erythematosus: Systematic review and report of three cases. Clin Neurol Neurosurg. 2015;128:17-24.
59. Lin N et al. Angiogram-negative subarachnoid hemorrhage: Relationship between bleeding pattern and clinical outcome. Neurocrit Care. 2012;16(3):389-98.
60. Mimori A et al. Subarachnoid hemorrhage and systemic lupus erythematosus. Lupus. 2000;9(7):521-6.
61. Kelley RE et al. Cerebral transmural angiitis and ruptured aneurysm: A complication of systemic lupus erythematosus. Arch Neurol. 1980;37(8):526-7.

Coming soon.

EMJ provides influential articles, presentations of scientific research and clinical practice, and in-depth reviews of international medical congresses.

Subscribe to *EMJ Hematology* for free.

EUROPEANMEDICAL-JOURNAL.COM /SUBSCRIBE

Buyer's Guide

- ABBVIE
- ALPINION MEDICAL SYSTEMS
- AMGEN (EUROPE) GMBH
- ARTHREX GMBH
- BIOGEN INTERNATIONAL GMBH
- BOEHRINGER INGELHEIM
- BRISTOL-MYERS SQUIBB
- BÜHLMANN LABORATORIES AG
- CELGENE
- CELLTRION HEALTHCARE
- DS MEDICA SRL
- ELI LILLY AND COMPANY
- EXPANSCIENCE
- EYELED GMBH
- F. HOFFMANN-LA ROCHE LTD.
- FIDIA FARMACEUTICI SPA
- FRESENIUS KABI LTD.
- GE HEALTHCARE
- GILEAD SCIENCE, INC.
- GLAXOSMITHKLINE
- GRIFOLS
- GRÜNENTHAL GMBH
- HEMICS
- IBSA INSTITUT BIOCHIMIQUE SA
- JANSSEN PHARMACEUTICA NV
- LCA PHARMACEUTICAL
- LG CHEM
- MEDAC
- MENARINI GROUP
- MSD
- NORDIC GROUP BV
- NOVARTIS
- PFIZER
- REGENERON
- SAMUMED, LLC.
- SANDOZ
- SANOFI GENZYME
- TILMAN
- UCB
- XIRALITE GMBH

VIEW CONGRESS REVIEW ←