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Contents

"A wide range of novel topics related to clinical, translational, and basic science were broached, including innovation in the population and rheumatological health services."

Spencer Gore, CEO

Editorial Board

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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.

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Front cover and contents photograph: Madrid, Spain, home of the EULARI 2019. © Watcharakorn Chotigo / 123rf.com

EMJ Rheumatol.

EMJ Innovations 3.1

View some of the latest advances and innovations from across the medical sphere and details their implications for treatment, education, and research.

VIEW ALL JOURNALS ←

Welcome

It is with great pleasure that I once again welcome our readers to another exciting edition of *EMJ Rheumatology*, bringing you the latest cutting-edge developments in this ever-changing field. In addition to our hand-picked selection of peer-reviewed articles and abstract reviews, I am proud to introduce our review of this year's European League Against Rheumatism (EULAR) Annual Meeting, held in one of our favourite cities: Madrid, Spain. This has been an exciting journal to prepare, a feeling we hope to instil in each of you as you read this edition.

As always, our team were on-hand to represent the journal at this year's EULAR meeting, attending numerous engaging sessions and talking face-to-face with global leaders in the rheumatology field. This year's event was in partnership with the Paediatric Rheumatology Society (PReS), helping to develop a programme that encompasses the complete spectrum of rheumatological disease. A wide range of novel topics related to clinical, translational, and basic science were broached, including innovation in the population and rheumatological health services. Its excellent programme appealed to a large audience, from veteran scientists to fledgling clinicians, and served as a promising sign for future EULAR congresses.

It was brilliant to hear from young and aspiring researchers at the event through countless poster and abstract presentations. In this edition, we include our selection of abstract reviews prepared by the authors themselves, such as an analysis of whether decision support systems can accelerate rare disease diagnosis, and a study in which the efficacy of a new rheumatoid arthritis-targeting, anti-fractalkine monoclonal antibody is determined.

This year's edition includes a number of peer-reviewed articles covering a diverse range of rheumatological topics. These include a fantastic mini-review of postmenopausal osteoporosis, an update on the diagnosis and anticoagulant treatment of antiphospholipid syndrome, and a discussion regarding the similarities and differences between two morphologically distinct conditions, polymyalgia rheumatica and seronegative elderly-onset rheumatoid arthritis. At EMJ, we continually strive to provide varied and engaging content across our 16 therapeutic area journals, and *EMJ Rheumatology 6.1* is no exception.

As always, I would like to send my gratitude and appreciation to everyone who has contributed to this journal for making it such a success. Rheumatology is a field filled with brilliant minds and passionate investigators, and as such is always a field that we take a lot of pride in tapping into to produce our annual journal. If you enjoy the work presented here and are eager to find out how to be a contributor to the growing EMJ family, please do not hesitate to reach out to us. Until then, enjoy our latest publication.

Spencer Gore

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Chief Executive Officer, European Medical Group

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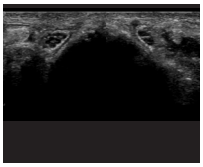

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Imagination at work

Foreword

Dear colleagues,

It is with great pleasure that I welcome you to this year's edition of *EMJ Rheumatology*, including a fantastic selection of peer-reviewed articles and highlights from the European League Against Rheumatism (EULAR) 2019 Congress in Madrid, Spain.

EULAR was once again a hotbed of ideas and discussion that undoubtedly pushed the field forward, serving as a framework to which scientific, clinical, and patient-orientated information regarding the treatment of rheumatic disease could be shared. There were a number of important developments shared for the first time at this year's congress, including an illuminating study in which electro stimulation was successfully implemented in rheumatoid arthritis patients for improvement of their symptoms. Rheumatic diseases are often defined by the difficulty that we as healthcare professionals, clinicians, and researchers have in finding therapeutic targets or treating, meaning that it is now more important than ever to seek new and innovative ways to alleviate global patient burden.

This is a journal of many personal highlights. Mondal et al. discuss the current status of using secukinumab for the management of psoriatic arthritis, providing an in-depth account of the relevant clinical trials that should be of particular interest to my colleagues in the clinic. The increasingly hot topic of immunometabolism is given centre-stage in an excellent review by Wincup et al., a prime example of the sort of outward thinking that is required by our field towards finding clinically viable therapeutic options for patients. Modulating the metabolome represents a ubiquitous target across multiple pathologies, making it all the more exciting a prospect for collaborative focus. Manzo and Emamifar also contribute a piece distinguishing seronegative elderly-onset rheumatoid arthritis and polymyalgia rheumatica, an invaluable aid in the diagnosis of the vulnerable elderly demographic to which these two conditions can be so prevalent.

Effective treatment of rheumatic disease requires wide-spread improvement across the entire healthcare spectrum, including diagnosis, management/support of the patient, and the targeting of efficacious treatments to robust targets. This is a real challenge, but one that we must meet head-on with vigour and passion, both attitudes that are obvious throughout this year's *EMJ Rheumatology* edition. I am confident you will agree with me as you read through this journal's 6th rheumatology edition: Enjoy!

Yours sincerely,

Dr Hector Chinoy
University of Manchester, UK

Congress Review

Review of the European League Against Rheumatism (EULAR) Congress 2019

Location: Madrid, Spain – Feria de Madrid

Date: 12th – 15th June

Citation: EMJ Rheumatol. 2019;6[1]:10-23. Congress Review.

This year's European League Against Rheumatism (EULAR) congress opened with an inspiring presentation from EULAR president Prof Hans Bijlsma and host Anna Pla Català at the impressive opening ceremony. Prof Bijlsma expressed his excitement about the congress, which was to be jam-packed with 125 sessions, 5,000 abstracts, a plethora of networking opportunities, and much more for the >14,000 delegates from around the world. "It's not only the quantity, but it's also a very high quality," he explained. Sessions were held on a wide range of topics to interest any rheumatologist, including epigenetics, reproductive issues, psoriatic arthritis, digital health, and myositis, to name just a few. For our pick of the top announcements and data releases, read our Congress Review highlights.

The city of Madrid was the backdrop to this year's EULAR congress, providing awe-inspiring views, a thriving culture, fascinating history, and delicious food and drink to complement the scientific advancements occurring in the congress centre. Prof Bijlsma commented on the clemency of the Madrid sunshine in comparison to the oppressive heat of an earlier congress, and hoped that delegates still chose to attend the sessions despite how beautiful it was outside! Sunbathing took second place though, as delegates swarmed to the lectures, interactive sessions, and abstract presentations on offer across the 4 days.

The quality of the sessions on offer was only increased by EULAR's collaboration this year with the Paediatric Rheumatology European Society (PReS) for the congress theme of 'Decades of Life'. In his welcome message to delegates, Prof Berent Prakken, PReS President, explained the common goal of PReS and EULAR being "To advance the care and improve the health and wellbeing of children and young people with rheumatic conditions." Following 25 years' worth of joint congresses, the two societies have this year developed this even further, creating a fully integrated joint

"The city of Madrid was the backdrop to this year's EULAR congress, providing awe-inspiring views, a thriving culture, fascinating history, and delicious food and drink..."

congress in order to help each achieve the very best in lifelong patient care. In his opening ceremony discussion, Prof Bijlsma talked of the great things that EULAR and PReS can learn from one another in this endeavour. To learn more about this collaboration and about PReS, read our interview with Prof Prakken here.

Just as in previous years, outstanding abstract presentations and research was recognised in a large number of awards at the congress. Undergraduate Abstract Awards were presented to the first authors of the highest scored basic science abstracts, this year awarded to Roline Krol, Huiyi Zhu, and He Chan. Basic Science Abstract Awards were awarded to Olivier Malaise, Richard Stratton, John Bowes, Kate Duffus, Remy Pollock, and Anastasia Filia. The Clinical Science Abstract Award winners were Lianne Kearsley-Fleet, Ai Li Yeo, Md Yuzaiful Md Yusof, Fenne Wouters, Hirotaka Matsuo, and Anna-Maria Hoffmann-Vold. In the category for Health Professionals' Abstract Awards, the winners were Ross Wilkie, Else Merit H Gravås, and Lindsay Bearne. Tinja Saarela was also recognised by EULAR in the People with Arthritis/Rheumatism across Europe (PARE) category for the highest scoring abstract submitted by a PARE member. The Foundation

"In his opening ceremony discussion, Prof Bijlsma talked of the great things that EULAR and PReS can learn from one another in this endeavour."

for Research in Rheumatology (FOREUM) this year gave an award for the first time for the best abstract related to a FOREUM-funded project, and awarded this to Juan L. Garrido-Castro.

It was a privilege for the EMJ team to once again attend this world-class event and to be able to report on the very latest cutting-edge research in the ever-evolving field of rheumatology research. We hope you will enjoy the highlights we have picked out and that we will once again see you in attendance at the EULAR congress 2020, in Frankfurt, Germany!

EULAR 2019 REVIEWED →

Rheumatoid Arthritis Could be Treated with Electrostimulation

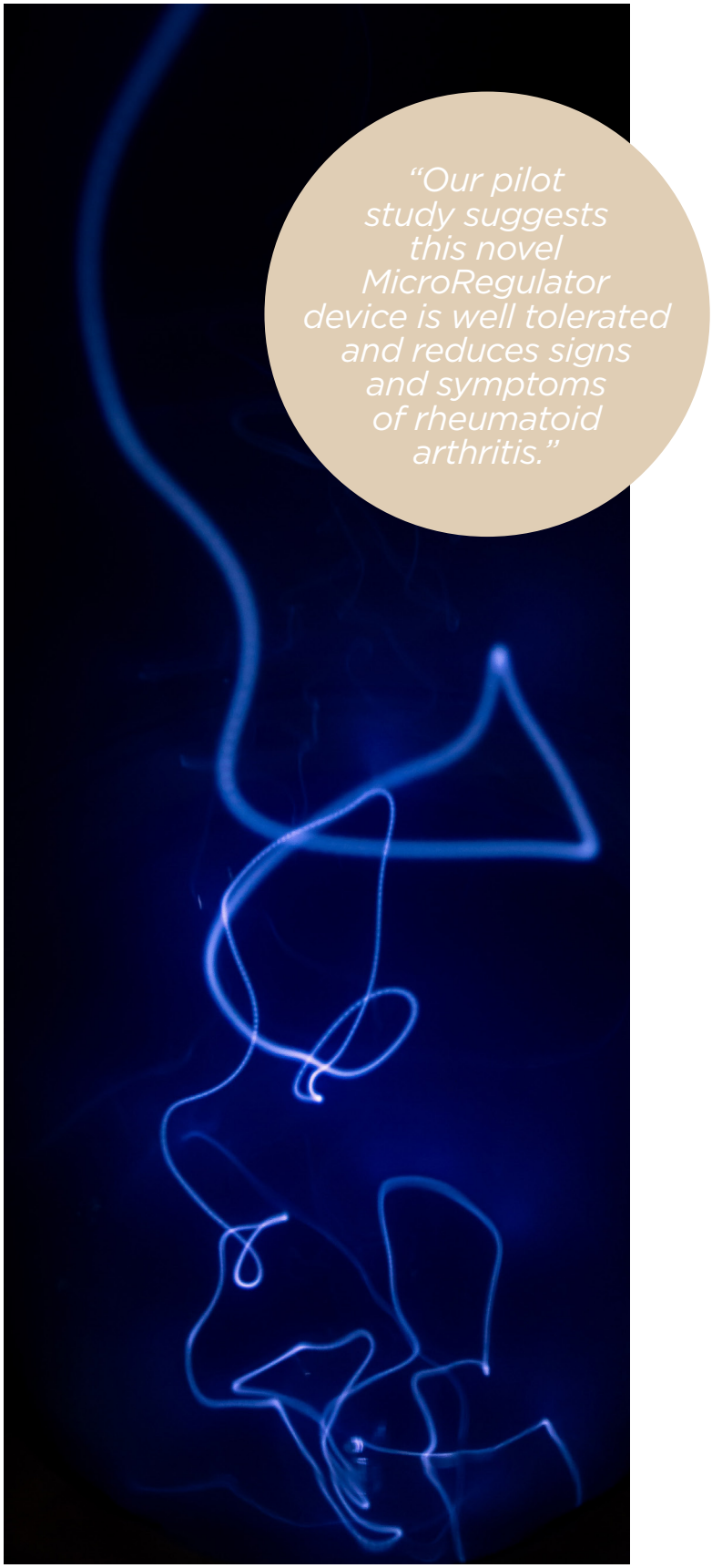
ELECTROSTIMULATION of the vagus nerve could be a potential treatment option for patients with rheumatoid arthritis. Research presented at the EULAR annual congress, and reported in a EULAR press release dated 14th June 2019, outlined results from a pilot study that tested a MicroRegulator neurostimulator on the vagus nerve: the longest and most complex of the cranial nerves, which helps to connect the brain to the body.

Rheumatoid arthritis has limited treatment options, as discussed by Prof Thomas Dörner, Chairperson of the Scientific Programme Committee, EULAR: "For many patients suffering from rheumatoid arthritis, current treatments don't work, or aren't tolerated." The results of this study showed a promising improvement in rheumatoid arthritis activity.

For the study, the researchers implanted MicroRegulatory, a miniaturised neurostimulator, into 14 patients who had rheumatoid arthritis, all of whom had failed on >2 targeted oral or biologic therapies. The patients were randomly assigned to one of three groups: placebo, stimulation once per day, or stimulation four times per day. After 12 weeks, two thirds of the patients who were in the once per day group met the EULAR 'good' or 'moderate' response criteria, showing a mean change of disease activity score 28-joint count C reactive protein of -1.24, considerably higher than the placebo group score of 0.16.

These results are promising in the future of the treatment of rheumatoid arthritis, as discussed by researcher Mark Genovese, James W. Raitt Endowed Professor of Medicine, Stanford University, Stanford, California, USA: "Our pilot study suggests this novel MicroRegulator device is well tolerated and reduces signs and symptoms of rheumatoid arthritis."

The team recognised the need for further research and Genovese went on to discuss the opportunities and implications of this pilot study: "These data support the study of this device in a larger placebo-controlled study as a novel treatment approach for rheumatoid arthritis and possibly other chronic inflammatory diseases".



Cyprus Sees Creation of a Rheumatology Nurse Programme

RHEUMATOLOGY nurse training has been incorporated into a programme for the first time in Cyprus. The patient organisation Cyprus League Against Rheumatism (CYPLAR) challenged the Cypriot government to create the programme to support people living with rheumatic diseases. News of the campaign was reported in a EULAR press release dated 14th June 2019.

Rheumatology has seen significant improvement in recognition as a nursing speciality in many countries, but Cyprus initially denied the introduction of the programme owing to a perceived lack of interest surrounding education in the field. CYPLAR met with the Government Nursing Services on several occasions to highlight the value of rheumatology nurses, which led to the creation of the 'Patient Care with Rheumatic Diseases' programme which was offered to 27 nurses in 2018.

The programme took place 1 day a week for a period of 3 months and included lectures by CYPLAR. Experience in preparing and delivering biologic and biosimilar therapeutics was gained in the 3 days in an outpatient rheumatology clinic and 1 day in a care department. Students then underwent examination: a case study presentation and a final written evaluation.

Subsequent to the training, participants were asked to complete a survey; the results were promising. In answer to the question 'After training, will you be interested in working as a rheumatology nurse in a rheumatology clinic?', 100% of the participants answered 'Yes'. Ms Andri Phoka Charalambous, Patient Expert General Secretary of CYPLAR, discussed the success of the campaign: "We're proud to have achieved a significant step towards our goal with the successful implementation of the first rheumatology nurse educational programme in Cyprus."

A study presented at EULAR supports this campaign. The randomised-controlled trial demonstrated how nurse-led patient education can be pivotal in improving essential safety skills in patients who have inflammatory arthritis.

The study comprised 120 patients who had rheumatoid arthritis, peripheral spondyloarthritis, or axial spondyloarthritis when they first received a biological disease-modifying antirheumatic drug. Patients were randomised into two groups: usual care or intervention care, which consisted of a face-to-face patient education session led by a nurse at baseline and after 3 months.

After 6 months, the acquisition of safety skills was assessed using the Biosecure score on a 0–100 scale: a questionnaire composed of 55 questions assessing their ability to deal with infection, fever, vaccination, and daily life occurrences. A significantly higher score was seen in the intervention group than in the usual care group at 6 months: 81.2+13.1 compared with 75.6+13.0, respectively (p=0.016). At baseline, the intervention had a mean duration of 65.5+17.9 minutes and 43.7±18.7 at 3 months. Intervention group patients also displayed a significantly better ability to cope with arthritis than the usual care group.

Catherine Beauvais, University Hospital Saint Antoine, Paris, France, concluded: "Safety is an important issue in the management of inflammatory arthritis treated with biologic disease-modifying antirheumatic drugs [...] We hope our results provide evidence to support the implementation of nurse-led patient education programmes in centres across Europe."

Risk of Rheumatoid Arthritis Increased by Certain Diseases

RISK of developing rheumatoid arthritis (RA) is significantly higher in individuals who already have Type 1 diabetes mellitus and inflammatory bowel disease (IBD), a EULAR press release dated 14th June 2019 reports. It is hoped the findings of a recent study will lead to an improved understanding of disease development and progression in RA, as well to help identify people at high risk of the condition earlier.

"...our results suggest that IBD and Type 1 diabetes may predispose to RA development, which merits further study,"

In the analysis, substantially more cases of IBD and Type 1 diabetes mellitus were present in RA patients compared with controls (1.9% versus 0.5%, p<0.001 and 1.3% versus 0.4%, p=0.01, respectively). "While it is common for patients to have both Type 1 diabetes and RA, our results suggest that IBD and Type 1 diabetes may predispose to RA development, which merits further study," outlined Dr Vanessa Kronzer, Mayo Clinic School of Graduate Medical Education, Rochester, Minnesota, USA. The team additionally observed that comorbidities occurred significantly more frequently in RA patients compared with controls following diagnosis of RA, despite levels being the same prior to diagnosis. This included venous thromboembolism and epilepsy, in which the differences between the two groups indicated them to be novel comorbidities for RA patients (10.0% versus 6.0%, p<0.001 and 3.0% versus 1.0%, p=0.003, respectively). Heart attacks were also more common in RA patients (3.8% vs. 1.2%, p<0.001) although high levels of cholesterol were less frequent in this cohort compared with controls (11.4% versus 16.4%, p=0.004). No differences were seen in the rate of cancer between the groups.

The researchers used a biobank to obtain data of 821 RA patients, each of whom were matched with three controls who were determined by age, sex, and location of residence at the time of the biobank survey. The mean age of the subjects was 62 years, and 73% were female.

"These results are important because understanding the timeline of comorbidity development in patients with RA will inform our knowledge of disease progression and help identify targets for improving outcomes," commented EULAR President Prof Hans Bijlsma.

Room for Improvement in Rheumatoid Arthritis Care

MAJOR gaps in care provided for rheumatoid arthritis (RA) patients across Europe have been outlined in a large pan-European survey of patients and rheumatologists presented at EULAR 2019. The findings emphasise the need for a greater focus to be placed on translating research findings into clinical practice, particularly in poorer countries.

Of the standards of care (SoC) measured in the survey, 'diagnosis within 6 weeks' was of most concern to patients and rheumatologists alike (52% and 59%, respectively). Next was 'information about patient organisations' (40% and 38%), followed by 'training on aids, devices and ergonomic principles' (39% and 34%), 'vaccination-related information' (38% and 27%), 'receiving a schedule of regular assessment' (33% and 23%), 'information on adequate physical exercise' (35% and 20%), and 'availability of treatment plan' (35% and 18%). 'Adequate disease-modifying antirheumatic drug received' was the least problematic SoC for both patients and rheumatologists (8% and 3%). It was also highlighted that problematic gaps were reported more frequently by those patients with higher education and lower self-reported health.

"It is concerning to see so many problematic gaps reported across many essential aspects of RA care," commented Dr Rachel Meisters, Care and Public Health Research Institute (CAPHRI), Maastricht University, Netherlands. "We hope these results act as a loud wake-up call to services across Europe."

Countries with lower GDP levels had problematic gaps reported by rheumatologists more often than in medium or high GDP countries in around half of the SoC. In regard to patient, and most rheumatologist analyses, there was major variation across countries despite adjustments being made for individual characteristics.

"At EULAR, our aim is to reduce the burden of rheumatic diseases on the individual and society and to improve the treatment, prevention, and rehabilitation of musculoskeletal diseases within and across countries," stated Prof Thomas Dörner, Chairperson of the Scientific Programme Committee, EULAR. "These results highlight how far there is to go to translate the advantages elucidated through scientific study into the daily care of people suffering with these diseases."

Encouraging Results from Tildrakizumab in Psoriatic Arthritis Study

"WE WELCOME these promising results for tildrakizumab in patients with psoriatic arthritis," said Prof Hans Bijlsma, of the findings from a Phase IIB study that were presented at this year's EULAR congress and reported in a EULAR press release dated 14th June 2019. The results in question demonstrated that tildrakizumab is safe and efficacious in the treatment of psoriatic arthritis.

The study was a 24-week, randomised, double-blind, placebo-controlled, multiple-dose, Phase IIB study and enrolled 391 psoriatic arthritis patients who had ≥3 tender and ≥3 swollen joints. Participants were randomised to receive tildrakizumab 200 mg or placebo every 4 weeks, or 200 mg, 100 mg, or 20 mg every 12 weeks. Stable concomitant methotrexate or leflunomide use was permitted but not mandated.

A 90% reduction in Psoriasis Area and Severity Index (PASI 90), and a 50% reduction in American College of Rheumatology response criteria (ACR50) was seen in significantly more of the patients who were receiving tildrakizumab at any dosage by Week 24 than the patients receiving placebo. The higher dosages elicited better responses but shortening the dosing interval of 200mg from 12 to 4 weeks did not demonstrate a measurable increase in skin or joint response scores. In the subgroup receiving 200 mg of tildrakizumab every 12 weeks, 79.6% and 50.0% of the patients achieved PASI 75 and PASI 90, respectively, compared to 16.7% and 7.1% in the placebo group, respectively ($p<0.0001$).

In total, 2.2% of tildrakizumab-treated patents and 2.5% of placebo-treated patients suffered serious adverse events (AE). The investigator judged that treatment-related serious AE were seen in 0.3% of tildrakizumab-treated patients. The most frequent of these were nasopharyngitis and diarrhoea with no reports of candidiasis, inflammatory bowel disease, major adverse cardiac events, or malignancy. No deaths were reported, and no patients discontinued treatment due to AE.

"Our results demonstrate a clear separation between tildrakizumab and placebo as early as 8 weeks," said Philip Mease, Swedish Medical Center/ Providence St. Joseph Health and the University of Washington, Seattle, Washington, USA. "A promising role is suggested for tildrakizumab in the treatment of patients suffering with psoriatic arthritis."

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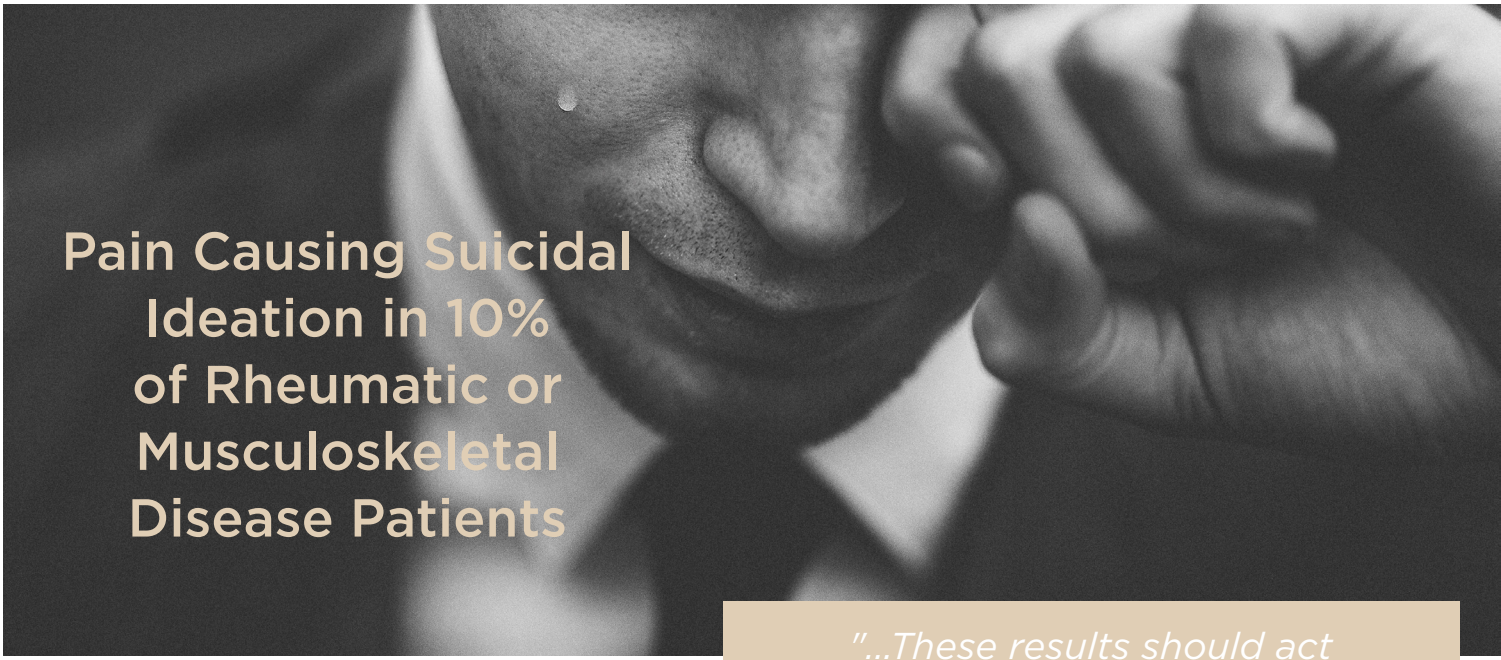


Pain Causing Suicidal Ideation in 10% of Rheumatic or Musculoskeletal Disease Patients

"...These results should act as a wake-up call to services across Europe"

PAIN caused by rheumatic or musculoskeletal diseases (RMD) has long been known to have a detrimental effect on mental health, but the extent of this impact on daily life has remained unclear. Now, a new survey performed by the Danish Rheumatism Association has reported that 10% of patients with these diseases had had suicidal ideation within the prior 4 weeks. This sobering data was presented in a press release on the 14th June 2019 at the EULAR congress in Madrid, Spain.

The survey was completed by >900 Danish patients who had ≥1 RMD, showing that pain had caused 58% of this cohort to feel that everything was unmanageable for them. This finding surrounding suicidal ideation warrants further investigation and increased psychological support.

A further discovery from this survey was the relationship between pain and sleep for these patients, with 69% reporting that their sleep quality had a negative impact on their pain; thus, two-thirds of patients reported never or rarely feeling fully rested, and 36% were taking painkillers to improve the quality of their sleep.

"Our study indicates that pain and poor quality of sleep have a huge impact on a patient's daily life, especially on their mental health," explained Ms Lene Mandrup Thomsen of the Danish Rheumatism Association. "We are using the results of this study in our political work to help campaign for better treatment and support for patients with chronic pain in our healthcare system."

For patients with RMD, pain is an ever-present factor in their life; 83% of these patients have pain daily or several times a week and 46% have received strong painkillers in the last year. The use of painkillers represents a significant problem for healthcare providers, and despite a strong focus by Danish authorities to limit their prescription, <25% of respondents had been offered an alternative solution to their pain.

"This survey highlights the huge importance of pain on the psychological well-being of RMD patients and the critical need to improve the support on offer. These results should act as a wake-up call to services across Europe," commented Prof Thomas Dörner, Chairperson of the EULAR Scientific Programme Committee.

This survey was not the only EULAR presentation to shed light on the impact of pain; another survey of 1,620 people with rheumatoid arthritis or adult juvenile idiopathic arthritis found almost a quarter to be experiencing clinical levels of anxiety or depression, >50% of whom had never received a formal diagnosis. Despite guidelines, it is clear that many RMD patients are not receiving the psychological support they need.

Time2Work Launched to Help the Unemployed with Rheumatic and Musculoskeletal Diseases

EULAR launched Time2Work on 12th June 2019, at the EULAR congress held in Madrid, Spain. Time2Work is a part of the ongoing 'Don't Delay, Connect Today' campaign and advocates better working environments for those with rheumatic and musculoskeletal diseases (RMD).

As the biggest cause of sick leave and premature retirement due to physical activity, RMD have a massive impact on individuals and the wider society, including productivity and the economy. The Time2Work campaign aims to raise awareness of these impacts and the importance of early diagnosis, early referrals to rheumatologists, and early access to effective treatments. It also seeks solutions to these challenges for patients and for the wider community.

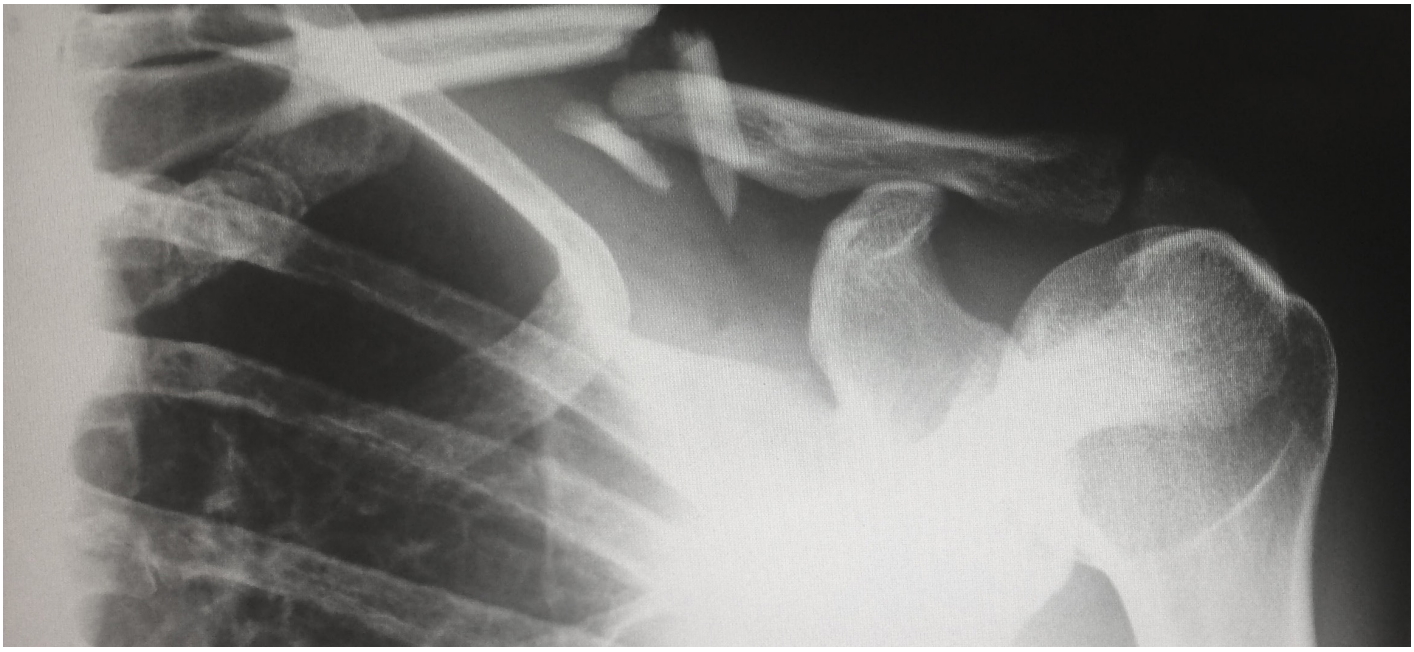
"Keeping people with rheumatic and musculoskeletal diseases in work not only benefits individuals, but also the whole of society,"

"Keeping people with rheumatic and musculoskeletal diseases in work not only benefits individuals, but also the whole of society," says Marios Kouloumas, EULAR Campaign Lead and President of the Cyprus League Against Rheumatism (CYLAR).

Time2Work contributes to the EULAR goal of increasing participation of people with RMD in work by 2023; if early interventions were more widely accessible for people with RMD, an extra 1 million employees could be in work everyday, reverting the considerable loss of productivity in the workplace that can be attributed to the employees' poorly supported RMD. Employers need to adopt inclusive workplace practices and provide support to RMD patients to allow them to remain in work.

"Work is a critical part of building self-esteem and it's a tragedy that so much talent is lost from the workforce," said Professor Iain McInnes, EULAR President Elect. "Today we call for three things: greater access to early interventions to limit the pain, tiredness, and immobility that make it difficult to keep working; greater awareness of the challenges people with rheumatic diseases face; and a review of the way we work. Small adjustments like flexible hours, improved access, home working, and standing desks could make all the difference."

Post-Denosumab Discontinuation Bone Mineral Density Loss Reduced



DENOSUMAB is a human monoclonal antibody used to treat osteoporosis by preventing osteoclast maturation, and its effect is limited to the period of drug exposure. Discontinuation of denosumab treatment is associated with severe adverse events in the bone including significant bone turnover rebound, rapid loss of bone mass, and a risk of multiple vertebral fracture. The results from a study presented at EULAR 2019 showed that the use of a bisphosphate, e.g., zoledronate, can significantly reduce this bone mineral density (BMD) loss seen.

The 71 participants in the study were classified into two groups: 'loser' (n=30) and 'stable' (n=41), relating to their BMD loss after denosumab discontinuation. 'Loser' patients were identified as having a BMD loss in the lumbar spine of >3.96% at 1 year post-discontinuation of denosumab.

Results from the study identified that the use of bisphosphonates prior to denosumab treatment was seen in 12% of the 'stable' group (p=0.047) versus none of the 'loser' group. Furthermore, that at initiation of denosumab, those in the 'loser' group were younger with a mean age of 61.4±7.3 years versus 65.5±8.2 years (p=0.034). In addition, the 'loser' group had higher levels of the bone turnover marker sCTX (644.7 versus 474.1 ng/mL; p=0.005).

"Our study suggests that being younger, having higher bone turnover markers, and not having received zoledronate before denosumab introduction increase the risk of bone mineral density loss following discontinuation of denosumab," summarised Dr Bérengère Aubry-Rozier, Rheumatology Unit, Lausanne University Hospital, Lausanne, Switzerland. "Our results support the use of denosumab after a bisphosphonate to reduce the bone mineral density loss at its discontinuation, and close monitoring of sCTX to maintain levels below the upper limit of the normal range for premenopausal women."

"Our study suggests that being younger, having higher bone turnover markers, and not having received zoledronate before denosumab introduction increase the risk of bone mineral density loss following discontinuation of denosumab,"

Psoriatic Arthritis Severity Linked to Increased Body Weight

"Our results highlight the impact of obesity and need for lifestyle-directed approaches to manage weight in psoriatic arthritis in parallel to joint and skin focused treatment."

FINDINGS were presented on the 12th June 2019 at EULAR attesting that BMI independently enhances the severity of the chronic inflammatory condition psoriatic arthritis (PsA). Whilst the disease had known increased prevalence in the obese and overweight population, to date few studies had investigated the relationship in detail.

Across 8 European countries, 917 PsA patients were pooled and had data collected regarding disease severity and impact as part of the PsABio study. The data were input into multiple regression models and adjusted for parameters such as sex, body surface area, and disease duration. Notably, BMI was shown to independently correlate to disability ($p<0.0001$), disease activity ($p=0.026$), and patient-perceived disease impact ($p<0.0001$). When obese patients were compared against non-obese patients, these parameters were again juxtaposed: disability measure HAQ-DI (range: 0–3) was 1.36 versus 1.03, disease activity measure cDAPSA (range: 0–10) was 33.4 versus 27.7, and patient-perceived disease impact measure PsAID-12 (range: 0–3) was 6.3 versus 5.3, respectively.

Dr Stefan Siebert, University of Glasgow, Glasgow, UK, commented: "Our results highlight the impact of obesity and need for lifestyle-directed approaches to manage weight in psoriatic arthritis in parallel to joint and skin focused treatment."

An additional two studies presented at the congress further demonstrated a link between BMI and another inflammatory rheumatological pathology. This analysis showed how the adipokine adiponectin can predict the manifestation of rheumatoid arthritis in overweight patients, in which raised serum adiponectin indicated a 10% increased risk of disease onset in a cohort of 492 subjects. Increased levels of these fat tissue-secreted signalling molecules, although shown in patients with rheumatoid arthritis, had not previously been validate for biomarker purposes.

Collectively, these studies highlight a potential therapeutic avenue that can be exploited for the diagnosis, management, and treatment of these rheumatological conditions.

Pain and Function in Hand Osteoarthritis Improved Through Prednisolone Administration

PREDNISOLONE, a glucocorticoid commonly used for treating inflammatory diseases such as lupus, rheumatoid arthritis, and polymyalgia, has been shown to significantly improve pain and function in patients with hand osteoarthritis at low doses. These results were presented on the 12th June at this year's 2019 EULAR meeting held in Madrid, Spain.

Synovial inflammation has previously been identified as a target for the treatment of hand osteoarthritis, a condition with significant disease burden and which is generally poorly managed in the clinic. However, due to limited conflicting data and lack of clinical evidence, prednisolone had not been recommended for patients as standard-of-care clinical procedure. Instead, treatment has primarily been limited to oral and topical non-steroidal anti-inflammatory drugs for the alleviation of pain.

Findings from the HOPE study appear to suggest that previous conceptions of prednisolone use for hand osteoarthritis may have been wrong, showing that 10 mg of the drug significantly improved average point difference in VAS finger pain (95% confidence interval: -26.1 to -6.9) and AUSCAN pain (95% confidence interval: -4.9 to -2.1, $p<0.001$) in a cohort of 92 patients with painful hand osteoarthritis. A total of 72% of patients treated with prednisolone were classified as responders using the OMERACT-OARSI response criteria, compared to 33% who received placebo. A reduction in synovitis was also observed following ultrasound of the prednisolone-treated arm.

"Significant improvements in pain and function were seen in the trial meaning prednisolone could be considered by physicians treating people suffering with hand osteoarthritis," commented Feline Kroon from the Leiden University Medical Center, Leiden, the Netherlands. By broadening the arsenal of pharmacological weapons that can be used for tackling hand osteoarthritis, one can assume that therapeutic measures can be optimised and that the overall clinical picture of these patients can improve over time.

"Findings from the HOPE study appear to suggest that previous conceptions of prednisolone use for hand osteoarthritis may have been wrong..."

PROmonitor

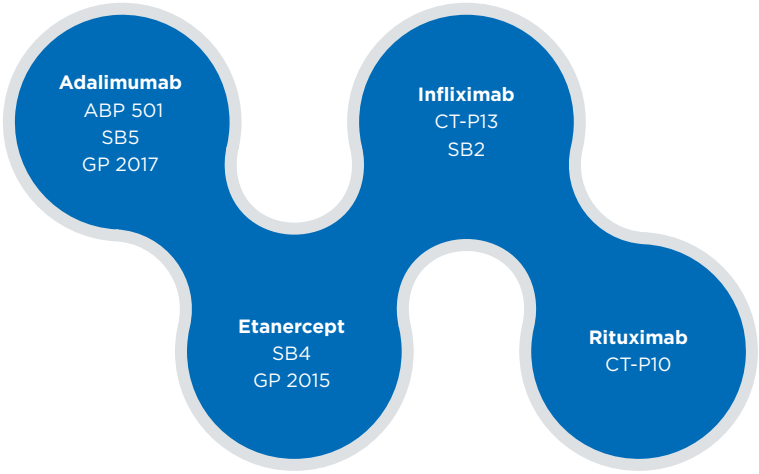
Therapeutic Drug Monitoring: A Real Need

Therapeutic drug monitoring is being increasingly adopted for the optimization of patient outcomes, particularly during maintenance treatment[1]

By providing TDM tools, clinicians may improve patient treatment strategy, reducing the risk of inadequate treatments, inappropriate dosages, and side effects[2].

A lack of information about serum drug levels and Anti-Drug Antibodies (ADA) can lead to non-optimal clinical treatment decisions and unnecessary costs[3]. Monitored treatments, along with the proper dose, are optimal and result in optimized cost allocation.[3]

Promonitor kits can quantify not only biological drug levels, but also biosimilar drugs [4,5,6,7]



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- Promonitor anti-Rituximab
- Promonitor Golimumab
- Promonitor anti-Golimumab
- Promonitor Vedolizumab
- Promonitor anti-Vedolizumab
- Promonitor Ustekinumab
- Promonitor anti-Ustekinumab

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Meet the Editorial Board

The world of rheumatology is evolving quickly, and the EULAR congress evidences the progress being made every year across the globe. We met with two members of the EMJ Rheumatology editorial board to discuss the future of rheumatology as well as their experiences, research, and professional goals.

Dr Lucía Silva-Fernández

Complexo Hospitalario Universitario de A Coruña (CHUAC), A Coruña, Spain

Q1 How does EULAR compare to other congresses that you have attended?

EULAR is much bigger than other congresses and meetings I usually attend, which are mostly at a national level. The science on offer is very broad, to a point that sometimes it can be impossible to see all the things you are interested in. The EULAR congress is also a great opportunity for working group meetings and generally a good chance to meet international peers working in the same field and establish new collaborations.

Q2 You were recently involved in research regarding 'Recommendations of the Spanish Rheumatology Society for Primary Antiphospholipid Syndrome.' What are the key take-home messages from part I and II of this research?

This was an initiative of the Spanish Society for Rheumatology to develop a set of recommendations on antiphospholipid syndrome in collaboration with other professionals involved in the care of these patients, such as haematologists and gynaecologists. The result is a document including 46 recommendations, which cover five main areas: diagnosis and evaluation, primary thromboprophylaxis, treatment of primary antiphospholipid syndrome or secondary thromboprophylaxis, treatment of obstetric antiphospholipid syndrome, and special situations. The document also includes information on the role of new anticoagulants, the recurrence of the disease, and the main risk factors for it.

Q3 How do you think we can work towards inspiring and encouraging more young women to consider a career in medicine?

Currently there are a lot of young women starting their career in medicine. In fact, in some medical schools in my country, the percentage of women among students reaches 80%. So, in principle the future of women in this field looks guaranteed. However, I see a much bigger and worrying difference in experienced professionals. Unfortunately, in most expert panels, committees, and working groups, the percentage of women is really low. Also, if we had access to a list showing

the leaders of major projects in rheumatology, we would find that women are underrepresented. Luckily, this situation is slowly changing, and in 2 years' time we will have the second female president in the EULAR's 70-year history. I think the only way of changing this situation is that the leaders and organisers of the different projects actively try to respect equality when designating the members of the committees.

"Luckily, this situation is slowly changing, and in 2 years' time we will have the second female president in the EULAR's 70-year history."

Q4 You chaired a poster session on Health Services Research. Could you share what the aims of the session were and were there any posters that stood out to you?

The session aimed to present different interventions in health services that could improve patient care. I considered all of them very interesting and useful, but I especially remember a poster from the UK on some measures to improve inpatient referrals and another from the USA on the impact of day of admission on mortality in septic arthritis. It was really interesting to see how circumstances other than the treatment or direct care of patients can have so deep an impact on their prognosis.

Q5 What advice do you have for young rheumatologists attending EULAR for the first time?

Attending EULAR for the first time can be overwhelming due to the large number of scientific sessions and other activities that are offered. The key to making the most of the congress is to carefully plan in advance what sessions and activities you want to attend. For this purpose, it can be very useful to download the EULAR Congress mobile App where you can plan your itinerary. Apart from the scientific content, I would also advise new attendants to set aside some time to explore other exhibition areas and take breaks. Once there, it is very enriching to start conversations with different people and engage in informal networking. In this sense, the poster viewing is a great opportunity to establish new contacts with colleagues with similar interests to yourself. Specifically aimed at young people, the Emerging EULAR Network (EMEUNET) has developed the Ambassador Programme, which consists of receiving congress mentorship from EULAR veterans in the same field of interest. For this initiative, they allocate 4–5 new attendants to an ambassador who contacts them before the meeting and guides them on how to choose among the different activities at the congress to make the most of their time. This programme has been running for a number of years and both the ambassadors and the first-time attendees are very satisfied with it.

Dr Suzanne Verstappen

Reader in Musculoskeletal Epidemiology, Centre for Epidemiology VERSUS Arthritis, Centre for Musculoskeletal Research, School of Biological Science, University of Manchester, Manchester, UK

Q1 Please can you tell us a little about your current research interests?

My main research interest is in rheumatoid arthritis and juvenile idiopathic arthritis. I focus on short-term and long-term outcomes and one of my main interests is in how these conditions affect work (absenteeism and presenteeism). I am the principal investigator of a large international study looking at presenteeism in Europe and Canada. I'm also the chair of the Outcome Measures in Rheumatology Worker Productivity Group: in this group, we recommend outcomes to be used in clinical trials and observational studies. Furthermore, I am a co-investigator of the VERSUS Arthritis/MRC Centre for Musculoskeletal Health and Work. Other areas of research include methotrexate. I am the chief investigator of a large methotrexate cohort from the UK including patients with rheumatoid arthritis who start methotrexate for the first time; we have about 2,400 patients included in that study with very detailed information on disease activity and patient reported outcomes, including work and adherence. We have also collected blood samples, genetic information, and more; it is a huge and very rich cohort.

Q2 Talking of your work on absenteeism, you recently co-authored a paper entitled 'A Systematic Review of Productivity in Economic Evaluations of Workplace Interventions: A Need for Reporting Criteria?' What would you say are the main take-home messages from this study?

I think work is an important outcome and I am therefore very pleased with the new EULAR campaign 'Time2Work'. We started to look more at absenteeism and presenteeism and there are a number of ways to measure presenteeism. However, these are not really developed to do economic evaluations, so if you want to do an intervention in the workplace, how can you then measure the loss of productivity? Our review shows that there is actually no real economic theory underpinning some of these measures and how the costs are calculated. So, there needs to be more consistency. If we really want to say this intervention is working (i.e., is cost beneficial or cost-effective) then we must create new measures, because it is currently very difficult to compare different interventions from an economic perspective.

"I am hopeful that attitudes towards study participation may change with future generations, so that research is generalisable to the whole population of interest."

Q3 Patient-centricity is a hot topic in the field of rheumatology. How important is this consideration and what problems does it pose for rheumatologists?

There a number of factors here playing a role and it has such a huge impact on many other things, including work, for example, and ideally some of these things should be taken into account. But we also know that there is always limited time for a rheumatologist and the general practitioner, for example, to discuss every single thing that may impact the patient. Perhaps it should be other people, like nurses and other health professionals, that discuss some of these topics. These topics might vary per patient, based on what they find important. So, for one person a key

consideration could be work, for another it might beforexampletheirfamilylife.However,Ithinkthatin general more people are more open to have that discussion in the clinic.

> "So, I think the focus for rheumatologists in the coming years should be a bit broader than just the disease itself, but on all the surrounding issues that are of paramount importance to patients."

Q4 What are some of your goals as the Director of Social Responsibility for the School of Biological Sciences at the University of Manchester?

The role includes a lot of things, including patient and public involvement and engagement. We do a lot of engagement events to inform the community in Greater Manchester about our research. Together with colleagues within the Centre for Musculoskeletal Diseases, we had a photography exhibition called 'The Future in Your Hands' celebrating people living with musculoskeletal conditions in Greater Manchester and highlighting how these people have taken control of their lives to live them the fullest.

Another aspect of social responsibility is what we call widening participation. We go out to schools in deprived areas and talk about research and about going to university; often these children do not even consider going to university. We have some really nice initiatives where we take a group of pupils from a deprived school to a field work centre in the Yorkshire Dales for a weekend. Most of these children have never been outdoors like this. During the weekend, we have several activities to talk about careers and about university life and what you can do with a university degree. During the weekend they will also do a number of field-work activities. These events not only inspire the students but are also an annual highlight for me.

Q5 On the topic of diverse backgrounds, what impact do factors like ethnicity and socioeconomic backgrounds play in your research?

Ensuring diversity within a study cohort can be challenging. For example, in the previously mentioned methotrexate cohort, we would expect that most participants are Caucasian. We used the UK Biobank, a large national study, wherein most participants classify themselves as White British. So, sometimes it can be very hard to recruit people from different backgrounds and ethnicities. There may be various reasons for this disparity; there may be a language barrier, for example, or other factors making it more difficult or less appealing for them to participate, or even that we simply do not record the data, such as in the case of socio-economic background in most studies. eHealth offers some solutions to this problem, but it also presents its own challenges: with eHealth you do not get the same level of detail as you get with a traditional observational study.

I am hopeful that attitudes towards study participation may change with future generations, so that research is generalisable to the whole population of interest.

Q6 What do you think will be the hot topics in rheumatology in the next few years?

From my perspective as an epidemiologist, there is still a need to gain a better understanding about the long-term outcomes (economic, quality of life, mobility, and others), especially with an ageing population and the fact that the burden of musculoskeletal diseases is increasing. Patients often have various conditions, and how these diseases interact to affect long-term outcomes is going to be very important. So, I think the focus for rheumatologists in the coming years should be a bit broader than just the disease itself, but on all the surrounding issues that are of paramount importance to patients.

Meet the Organisers

Each year, the EULAR congress continues to grow larger and larger. Ensuring an exciting and fulfilling programme is an enormous undertaking. We spoke to Mr Dieter Wiek and Prof Berent Prakken to discuss their roles in organising EULAR and their experiences at the congress.

Prof Berent Prakken

President of the Paediatric Rheumatology European Association (PRES), Professor of Paediatric Immunology and Vice Dean for Education at University Medical Center Utrecht, Utrecht, the Netherlands, and co-founder of the Eureka Institute for Translational Medicine

Q1 What first attracted you to a career specialising in paediatric rheumatology?

The drive to help children with a chronic disease cope with their condition, adapt to limitations, and live their best possible lives.

Q2 In what ways does paediatric rheumatology represent a unique challenge for the physician?

Compared to adult rheumatic diseases, juvenile rheumatic diseases hit the patient during growth and development, both physically and mentally. This brings special and unique challenges for the paediatric rheumatologist.

Q3 With an increasingly ageing population worldwide, what steps would you like to see put in place to encourage rheumatological health in the general population?

Obviously, we must support a healthy lifestyle. But this should not be a top-down hierarchy with us setting guidelines; it should not be one size fits all. Instead, I think we should actively involve patients in managing their own health; only through doing this can we develop true personalised medicine.

Q4 As President of PRES, you said your personal ambition is to "support the growth of the PRES community by strengthening the patient perspective, encouraging young talent, and by connecting PRES with the outside world". What steps has PRES taken to work towards these goals?

We have made many small but significant steps towards achieving this goal. These include redefining our mission, setting a strategic plan for the future (PRES 2025), and incorporating the European Network for Children with Arthritis (ENCA) as a patient organisation in PRES.

Q5 With PRES celebrating its 25th conference last year and now co-hosting the EULAR congress, this is an exciting time to be working in paediatric rheumatology. Do you think clinicians working in this field will become even more specialised in the future?

We will need so-called T-shaped professionals, who are both experts in their field and have also learned to navigate across boundaries and specialties.

"I think we should actively involve patients in managing their own health; only through doing this can we develop true personalised medicine."

Q6 The integration of paediatric rheumatology throughout the congress programme is excellent this year. How vital is the sharing of knowledge between PRES and EULAR and, given your role in planning the event, how did you decide what paediatric sessions to include in the programme?

I strongly believe that it is crucial we learn from adult rheumatologists, while I also feel that we have quite a lot of insight to offer to the EULAR community. Professor Michael Beresford, chair of the PRES scientific committee, did an excellent job in choosing the subjects that might be of interest for both communities. Having said this, choosing was extremely difficult; he could easily have filled twice as many sessions!

Q7 How has translational medicine shaped paediatric rheumatology treatment and care?

Paediatric rheumatology has a tradition in translational medicine and, in recent years, PRES has specifically supported this; for example, by supporting young investigators (which has led to the Emerging Rheumatologists and Researchers [EMERGE] group of young investigators) and by linking with the Eureka Institute for Translational Medicine. While in some other fields clinician scientists are 'threatened', they flourish in our field. We must make sure that we keep this positive momentum going, by actively supporting initiatives from clinician scientists.

Q8 You are the co-founder of the Eureka Institute for Translational Medicine. What is the mission of the institute and how do these ideas and goals interact with your work as President of PRES?

The mission of the Eureka Institute (www.eurekainstitute.org) is to develop a community of translational medicine professionals equipped to inspire and catalyse the application of discoveries for the benefit of human health. Eureka does this through education and building a community, especially concerning the training and education of our future leaders in PRES to ensure our goals are completely aligned. For that reason, PRES has supported talented individuals from our EMERGE group to participate at the summer school that Eureka organises in Utrecht, the Netherlands.

Q9 You have published >170 papers, are a regular reviewer for many journals, and sit on several committees and boards. With so many roles and responsibilities across the field, how do you stay motivated?

It is very easy for me to stay motivated as I am constantly in touch with my 'target audience': patients, students, and young investigators. Working with them shows me every day that there is still so much important work to do!

Q10 What advice would you have for a young paediatric rheumatologist just beginning their career in this field?

Relax, have fun, and enjoy the ride: it is the most rewarding job I can imagine.

Dieter Wiek

EULAR Vice President representing National PARE Organisations

Q1 What do you enjoy most about your role as Vice President of EULAR and a representative of the National Organisations of People with Arthritis/ Rheumatism (PARE)?

We see that there are discrepancies in European healthcare. So, it is great to support the initiatives of patient organisations to inspire better healthcare in their respective countries, but also to lobby for the interests of people with rheumatological diseases on the European stage, e.g., through the various EU institutions.

A key point is to talk to people with rheumatological diseases about their personal situation, so that I am aware of the aspects I am aiming to bring to attention in all these lobbying talks.

Q2 What are some of the challenges of the role?

The key challenge is that, as a volunteer, you have to invest a lot of time.

Q3 The missions of PARE are to improve patients' experiences by giving them a voice, developing strong networks, and creating alliances. How are PARE working towards achieving these goals?

It is a key principle of our PARE sessions to represent patients' experiences by, for example, presenting them at the EULAR Congress. The abstract sessions underline these experiences as well. For the Stene Prize, an annual award, patients write about their experiences on a predetermined topic.

Additionally, the Annual PARE Conference not only has educational purposes, but also enables networking and the creation of alliances. Other programmes, like the Knowledge Transfer or the Engagement Programme, also support these aims.

Q4 You have personally discussed the importance of patient engagement. How are you using your position at EULAR to try and encourage patient engagement and communication within rheumatology?

We are trying to engage our patients and colleagues in discussion through workshops at the Annual Conference, sessions at the Congress (e.g., 'How to get involved in Health Technology Assessment'), and through all our activities that support the involvement of patients in research, for instance through our Patient Research Partner network. These sessions encourage the cooperation of patients with clinicians and health professionals, with a focus being on patient engagement and communication in rheumatology.

Q5 You recently co-authored a paper on the conduction of rheumatology studies: "EULAR 'points to consider' for the conduction of workforce requirement studies in rheumatology". What are the main take-home messages from this paper?

We can see that in some countries there is a lack of rheumatologists, but it is not just the number that counts. When looking at the number, we have to take into consideration the general attitudes towards the scope of practice and work. In the future, we can also consider that e-health solutions may compensate for these deficits.

Q6 Is there a session that you are particularly looking forward to at this year's EULAR congress in Madrid?

PARE offers lots of great sessions. One of my favourites is this year's e-Health session, as it shows and discusses what personal gains for self-management and healthcare are possible through e-health and how the relationship between patients and health professionals has changed.

Q7 How important is the consideration of mental health in the treatment of rheumatic diseases?

In my opinion, non-pharmacological treatments should be regarded with higher importance than they have now. Apart from physical activities, physiotherapy, and other considerations, mental health should be a key aspect for self-management.

Q8 As a patient with ankylosing spondylitis yourself, how have you seen knowledge and treatment of the disease change since you were first diagnosed?

A patient's knowledge has definitely increased through online services, social media, and rehab programmes. But dissemination of knowledge does not mean that these guidelines and recommendations are followed. The point is this: how can we enable that knowledge to lead to sustainable action?

We still see that a person's diagnosis can be delayed, and this is a problem we have to overcome.

Nowadays, patients who are seriously affected, especially young patients, have a good chance that deformities will be prevented. Also, biologics mean patients have got a much better health outcome and can stay in work.

Q9 How has your experience as a teacher helped you in your role in the rheumatology industry?

Honestly, I do not feel I am in the rheumatology industry. I always regarded my task as a teacher to improve a young person's knowledge and equip her or him with the necessary skills and methods to be a positive and critical citizen. I see myself as a critical person trying to overcome deficits and improve the healthcare situation for patients. This can be achieved with the support of clinicians, and healthcare professionals.

Q10 What area of rheumatology do you hope to see gain more attention over the next few years?

I still hope that, with the help of testing or screening and appropriate treatment measures, it will one day be possible to prevent the onset of diseases like rheumatoid arthritis, ankylosing spondylitis, or Lupus.

"I always regarded my task as a teacher to improve a young person's knowledge and equip her or him with the necessary skills and methods to be a positive and critical citizen."

Optimising Patient Management in Rheumatoid Arthritis: Can We Live Up to Patient Expectations?

This symposium took place on 13th June 2019, as part of the European League Against Rheumatism (EULAR) Congress in Madrid, Spain

Chairpeople: Peter Taylor[1]

Speakers: Marco Matucci Cerinic,[2] Ulf Müller-Ladner,[3] Ruth Slack,[4] Thierry Thomas[5]

1. University of Oxford, Oxford, UK
2. University of Florence, Florence, Italy
3. Kerckhoff-Clinic, Bad Nauheim, Germany
4. West Suffolk Hospital, Bury St Edmunds, UK
5. University Hospital of Saint-Étienne, Saint-Étienne, France

Disclosure: Prof Matucci Cerinic has received speaker and advisory fees from Actelion, Biogen, ChemomAb, Johnson & Johnson, Janssen, Lilly Galapagos, MSD, Pfizer, and Sandoz. Prof Müller-Ladner has received speaker and advisory fees from Biogen. Ms Slack has received speaker and advisory board fees from AbbVie, BMS, Biogen, Gilead, Janssen, Hospira, Lilly, Novartis, Medac, MSD, Roche, and UCB. Prof Taylor has received research grants and consultation and/or speaker fees from AbbVie, Biogen, Celgene, Eli Lilly and Company, Galapagos, GSK, Janssen, Nordic Pharma, Novartis, Pfizer, Roche, Sandoz, Sanofi, and UCB. Prof Thomas has received research grants and consultation and/or speaker fees from AbbVie, Amgen, Arrow, Biogen, Bone Therapeutics, BMS, Chugai, Laboratoires Expanscience, Gilead, HAC-Pharma, LCA, Lilly, Medac, MSD, Novartis, Pfizer, Theramex, Thuasne, TEVA, and UCB.

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This is a summary of a Biogen and Samsung Bioepis-sponsored satellite symposium at the EULAR Congress, held in Madrid, Spain, on 13th June 2019.

Citation: EMJ Rheumatol. 2019;6[1]:33-40.

Meeting Summary

In a highly interactive symposium, a multidisciplinary faculty from across Europe assembled to discuss how best to meet the expectations of patients with rheumatoid arthritis (RA) in an increasingly complex therapeutic landscape. The introduction of biologic therapies and, subsequently, their biosimilars have been of great importance in improving treatment outcomes and have had a considerable impact on many healthcare economies. As more biosimilars are approved, the expert panel discussed how patients with RA can be treated more effectively during the early window of opportunity, which may lead to sustained remission, prevention of structural damage to bones and joints, and provision of more quality-adjusted life years to patients while simultaneously offering major savings for healthcare systems.

Introduction

Anti-TNF biologics have revolutionised treatment of RA. More recently, the emergence of high-quality biosimilars has provided a cost-effective means of prescribing biologic therapies to eligible patients. However, clinical challenges persist including practicalities of switching, from both a patient and physician's perspective, in addition to dealing with healthcare economic systems to ensure that eligible patients have access to the most effective treatment in a timely manner. Patient expectations are at the very centre of decisions regarding disease management, and meeting these is a key feature of measuring treatment success. In this symposium, the basis for drug selection in an increasingly busy landscape was discussed. The introduction of biosimilars, which offer patients with rheumatic diseases earlier and more sustained treatment, increasing the probability of long-term remission with less cost constraint was highlighted. Best practices for managing and meeting patient expectations in different healthcare economies were considered by an expert, multidisciplinary faculty from across Europe.

Treatment Choice in Rheumatoid Arthritis: The Therapeutic Landscape

The current therapeutic landscape in RA was outlined by Prof Taylor, who described the evolution of treatment. A generation ago, the only available disease-modifying antirheumatic drugs (DMARD), such as methotrexate, leflunomide, sulfasalazine, cyclosporine A, gold, hydroxychloroquine, and glucocorticoids, were of the conventional synthetic type (csDMARD). Biologic therapies were first approved in the late 1990s; however, largely due to cost constraints, many healthcare economies do not offer the early use of biologics, even when csDMARD do not achieve the therapeutic target of disease remission.

Prof Taylor noted the complexity of biologic therapies due to their size, the need for living organisms to produce them, and tightly controlled manufacturing process when compared with small-molecule drugs. He therefore emphasised that different batches of the same biologic exhibit great similarity but are not exact replications.

With patents for reference biologic therapies expiring, biosimilars have emerged on the market. Approval processes, including the demonstration of their biosimilarity, are rigorous, and there are abundant data supporting equivalence in terms of the efficacy and safety of biosimilar molecules compared with their reference products. Prof Taylor said that, in light of this, a challenge faced by prescribers is deciding which biosimilar to select for a patient, especially while choice increases as new products become available.

What are the Drivers of Drug Selection?

Prof Taylor outlined aspects of treatment that need to be considered when prescribing in RA (Figure 1). Biological factors include the length of time with disease, disease stage and activity score, number of previous therapies, and existing comorbidities. More established disease can be associated with comorbidities such as cardiovascular disease, lung and ocular involvement, inflammatory bowel disease, and depression. As such, treatment must be chosen carefully to avoid development or exacerbation of the aforementioned.

Patient choice is also an important consideration. Their preference of administration route and their individual lifestyle are factors that should be taken into account, particularly concerning whether or not they are comfortable using needles. Prof Matucci Cerinic expressed the need to listen carefully to the patient's expectations for treatment and to make an informed, shared decision. However, it is also necessary to evaluate the safety, tolerability, and immunogenicity of each drug, along with efficacy and adherence rates.

While all of these are factors in the decision-making process, cost is also a major driver of treatment selection and often limits the selection of the most appropriate treatment in a timely manner. Profs Matucci Cerinic, Müller-Ladner, and Thomas confirmed that in their experience in Italy, Germany, and France, respectively, authorities are concerned about the expense of prescribing.

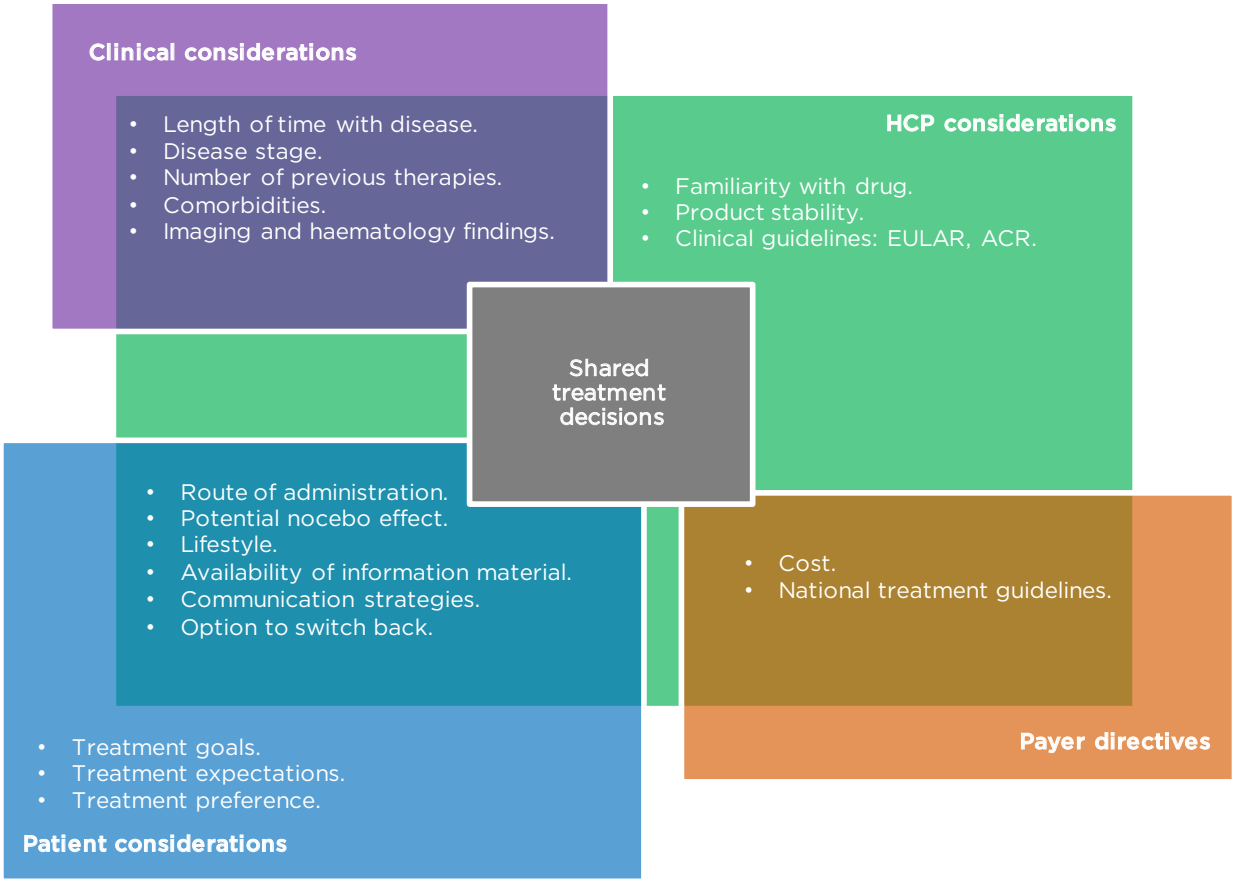

Figure 1: Many factors in multiple domains overlap to influence treatment decisions in RA.

ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; HCP: healthcare professionals; RA: rheumatoid arthritis.

Different countries' healthcare economies have different guidelines, but all limit treatment options to the most cost-effective therapies to some extent.

An audience poll revealed that cost considerations were the most important non-medical factor influencing their treatment decisions (40%), although this was closely followed by familiarity with a drug (33%). Prof Müller-Ladner commented that drug familiarity entailed knowledge of its price and how the product works, and is important not only for physicians, but also for others involved in care including nurses and the patients themselves.

Choosing Between Biosimilars of the Same Reference Product to Meet Patient Expectations

Prof Müller-Ladner discussed the crowded anti-TNF biosimilar landscape, with five adalimumab, three infliximab, and two etanercept products currently approved by the European Medicines Agency (EMA), with many more in development. He reiterated the concept of demonstrating similarity in both non-clinical and clinical studies comparing products sourced from multiple countries before being approved for use. This increasingly busy field of nearly identical biosimilar products makes differentiating between them difficult.

Product attributes such as physical, chemical, and biological stability have implications for the selection of biologic medications. In a study involving 255 patients, only 7% of participants

stored all biological DMARD (bDMARD) packages within the Summary of Product Characteristics (SmPC)-recommended temperature range.[1] Different adalimumab biosimilars have different approvals for storage duration both within and outside the cool chain; a longer, approved stability outside the cool chain may be beneficial to patients who travel for extended periods of time, for example. Other differences between currently available adalimumab biosimilar products include needle gauge, injection volume, presence of citrate in the formulation, and latex components in the device. The delivery device can be a pre-filled syringe or an autoinjector pen, and different marketed products have unique characteristics. Prof Müller-Ladner noted that these small variations may make a significant difference: a slightly larger needle gauge may cause more pain to the patient and reduce their adherence, and a latex allergy will disqualify certain patients from certain products. He recommended that if a patient fares less well on a particular therapy, the physician returns to a consideration of all features of a particular product to find one that the patient prefers.

Prof Müller-Ladner suggested that flexibility is also important in selecting the administration device and that patients should be given an opportunity to return to the clinic if their expectations are not being met. He also remarked that physicians themselves may never have seen the devices that they are prescribing for patients and recommended that all healthcare professionals (HCP) familiarise themselves with the physical delivery devices. This, he noted "is one of the little details of prescribing behaviour that you can refine to benefit your patients."

Prof Thomas spoke about the importance of the confidence that prescribing physicians have in biosimilars. Although it is an integral part of the doctor's role, he identified a particular need for transferring confidence during a switch from a reference product to a biosimilar and in "giving a fair explanation" for this occurrence. This strategy may be helpful in setting patient expectations at a reasonable level prior to commencing therapy, thereby increasing the chance that they will be met.

The Nocebo Effect: When Patient Expectations Affect Outcomes

The fact that biosimilars are mostly prescribed for cost-saving reasons may lead a patient to believe that there is a reduction in quality that comes with this, meaning that they are potentially more vulnerable to being associated with a nocebo effect. When a patient has negative expectations of a therapy, psychogenic adverse events or lack of efficacy may be noted.[2]

Prof Taylor described a Finnish study in which patients were started on a biologic treatment shortly after they began to emerge onto the market for the first time.[3] Functional and disease activity scores (DAS) were measured. The results were compared with those from another cohort who had started the same therapeutic 10 years later. DAS and functional scores were comparable, but a discrepancy was seen in the patients' satisfaction with the treatment, with patients in the initial cohort reporting significantly higher satisfaction levels compared with the second treatment group. It is suggested that this was due to increasing patient expectation.

In an audience poll, 39% of respondents reported identifying a potential nocebo effect in <20%, and 23% reported seeing it in >20% of their patients. A total of 19% of respondents were not sure whether they had encountered it and the same proportion reported that they had not. Language and mannerisms used in communication are equally important. 'Positive framing', which involves reassuring the patient and sharing data reinforcing efficacy alongside adverse event information, can be employed to instil further patient confidence in the treatment and prevent negative expectations, therefore mitigating a potential nocebo effect.

Individual words, too, can have an impact on outcomes via the nocebo effect. For example, for some patients, 'cheaper' may connote inferior quality and, therefore, describing biosimilars in terms of 'cost-effectiveness' could help to reduce nocebo effects. Body language, too, can influence a patient's reaction to a new medication.[4]

An audience member asked how it is possible to be certain that any problem is a result of the nocebo effect and not an issue with the drug itself. Prof Taylor suggested that, by virtue of being

a biosimilar, a therapy will have demonstrated equivalence to the reference product in rigorous preclinical and clinical trials. He pointed to further evidence of expectation bias bringing about a nocebo effect in other studies involving switches between non-biologic drugs in different therapy areas.[5-7] Nevertheless, Prof Taylor noted that even with cohort-level evidence, there remains a responsibility to treat every patient individually and to consider alternatives if a patient is not responding optimally having switched to a biosimilar.

Providing Switch Information: Setting Reasonable Patient Expectations

Echoing Prof Matucci Cerinic's sentiment, Ms Slack agreed that, in an ideal world, all treatment decisions would be shared between the physician and the patient, with all therapy options available to choose from. However, similar to the situation in the other countries represented, health authorities in the UK have restricted biologic prescribing and issued directives to switch all patients on biologic drugs to biosimilars. Because of this, Ms Slack suggested that it was a situation "not so much about informed decisions, but about informed consent" to switch. She highlighted the importance of openness with the patient about the reasons for the switch, and making all the relevant information accessible to the patient.

How information is communicated to patients is crucial. Ms Slack referenced the position statement from the UK National Rheumatoid Arthritis Society (NRAS) regarding switching. Ideally, patients should have a face-to-face consultation with their HCP to discuss the switch, including the reasons, risks, and benefits. Prof Matucci Cerinic said that when his centre switched all patients from a reference product to its biosimilar, a successful strategy was to have a doctor reserved for the purpose of individually discussing switching with patients. He suggested that this proactivity was, in part, responsible for inspiring confidence and led to very high uptake rates, patient co-operation, and improved adherence rates.

Where individual consultations are not possible and the information must be communicated in writing, the reason for the switch should be made clear and a telephone number for queries should be provided. This was relevant to a question from an audience member who practised in Colombia and described her clinical practice, in which she may see 30 patients in a single morning. Prof Taylor also mentioned his centre's 'patient education sessions', where patients are able to ask questions to nurse specialists and talk with other patients to share experiences, and recommended this as an effective way to bring patients and clinicians together for discussion in a time-efficient manner.

HCP who are open, accessible, and can speak frankly about the switching process and reasons for it transfer confidence to patients and help to build trust in their treatment. This could lead to greater switch acceptance and adherence rates. Healthcare institutions are encouraged to prepare 'One Voice' packages, which provide standardised lexicon and language usage guidance for all staff to ensure that a unified and coherent message is given to the patient. Ms Slack reported that, in her experience, patients had inherent trust in their HCP and would usually not query medical issues surrounding the switching process; however, they were more concerned about the practical aspects. Concurrently, she said that, from her own experience, she would be reluctant to assure patients that assenting to a switch would have immediately tangible benefits, such as being able to fund additional clinical staff in the department. If the healthcare economic system in question did not proceed to reinvest savings directly then this could lead to patient expectations not being met. She emphasised the importance of reassuring patients that they would be able to switch back to the reference product if they felt that treatment with a biosimilar was leading to inferior outcomes. In a state-directed switching programme at her centre in the UK, she reported that only 3 out of 200 patients refused a switch, but that the assurance of the option to return to the initial drug was an important factor in obtaining consent.

The Therapeutic Window of Opportunity: Halting Disease Progression

Prof Matucci Cerinic presented a case study of a patient with early-stage RA who presented with high levels of circulating rheumatoid factor and anti-citrullinated protein antibodies. Sonographic imaging also indicated high disease activity. Current EULAR and American College of Rheumatology (ACR) recommendations suggest that csDMARD treatment should be commenced "as soon as the diagnosis of RA is made," with the aim of bringing about clinical remission. He presented data indicating that early csDMARD treatment significantly reduced progression of radiographic joint damage since symptom onset.[8] The faculty discussed current treatment algorithms. Prof Taylor noted that in patients with such poor prognoses, it would be ideal to introduce bDMARD into the combination therapy regimen as soon as possible. Prof Müller-Ladner suggested that the aim of treatment in this case should be "to stop the fire from spreading to the rest of the body," and said that "in this kind of patient, one should be allowed to have a combination right away." He added that it is always possible to remove bDMARD or csDMARD from the combination, but unfortunately, economic constraints in individual countries mean that this treatment is not available. This does vary between countries, however, and Prof Thomas noted that in France it is possible to introduce bDMARD into combinations early on, though not as first-line therapy.

In a poll, 75% of audience members agreed that the current treatment algorithms should be modified to allow use of biologics earlier in therapy pathways assuming cost is not an issue. An audience member asked whether "clinical guidelines should be driven only by clinical outcomes and not by cost… since that means that the right drug was being withheld based on economic considerations." Prof Taylor suggested that, beyond an ethical issue, it was also a societal and political one. He described the process in the UK, where the National Institute for Health and Care Excellence (NICE) must make decisions, on behalf of the country's entire population, on how to disseminate limited funds in the most beneficial way for all patients with all medical problems. He noted that making policymakers aware of ethical complications could initiate change, but that funds would have to be diverted from another source to secure this. Another audience question referred specifically to the position of NICE, and whether the body would change its position based on the more cost-effective nature of biosimilars. Prof Taylor confirmed that, currently, patients must have a 28-joint DAS of at least 5.1 before being considered for therapy with targeted agents, but that NICE were currently reviewing RA treatment guidelines and that this may change.

Therapeutic Drug Monitoring: Optimising Patient Management

During the meeting, the use of therapeutic drug monitoring (TDM) to inform decisions about therapeutic dose adjustment (dose tapering or dose intensification) was also discussed. Again, it was agreed that these considerations are usually driven by healthcare economics and not by dose limiting. Prof Taylor said that treat-to-target has revolutionised care, allowing for individualised treatment; however, most biologics do not have a dose-titratable range within licence. It may be possible to consider TDM as a means of pharmacological dose optimisation.

Prof Thomas outlined the reasoning and methodologies employed in TDM,[9,10] and presented data from the RETRO study.[11] This was a randomised controlled trial in which 101 patients with RA in stable remission continued DMARD treatment at the same level, tapered down to 50% of the original dose, or ceased the treatment after 6 months of the tapered dose. In the tapering or ceasing cohorts there was a significantly higher rate of relapse from the sustained remission disease state. However, at 1 year, approximately 60% of patients in the tapering cohort and 50% of those in the treatment cessation cohort remained in stable remission. Prof Thomas mentioned recent publications in which TDM was evaluated as a tool to inform successful tapering[12] and to optimise treatment selection in patients who had lost response to adalimumab.[9] If sufficiently high circulating drug levels are present following dose reduction then it is more likely that a patient will remain in sustained remission, suggesting that

TDM may be helpful in facilitating cost-effective treatment strategies.

Prof Matucci Cerinic recalled clinical scenarios in which patients were keen to taper or stop therapies, often requesting that methotrexate treatment be tapered or stopped instead of biologic treatment. He said that patient wishes would need to be taken into consideration, and agreed with an earlier proposition made by Prof Thomas suggesting a strategy of ceasing steroid and tapering methotrexate treatment prior to stopping biologic therapy. He also indicated that ending steroid treatment is often most beneficial for the patient in terms of adverse effects, and may therefore help to meet patient expectations effectively.

Ms Slack presented a case study on dose tapering, focussing on the expectations of the patient. Patients themselves are more likely to see their disease in terms of their quality of life and daily activities, not by numerical, clinical scores. In this case, a 56-year-old male had a number of personal goals that he wanted to achieve through treatment, including being able to climb stairs and cycle. After 6 months of treatment on methotrexate and treble DMARD therapy, he still had high health assessment questionnaire scores and DAS and was therefore eligible for biologic treatment.

Following 4 months' biologic treatment, his DAS was significantly reduced, he had returned to work part time, and had achieved all his personal goals. He expressed a desire to reduce the burden of his regimen, and the nursing team advised him on a strategy for this: reducing methotrexate and csDMARD dosages while maintaining the bDMARD regimen, correlating with the recommendations of Prof Thomas and Prof Matucci Cerinic earlier in the symposium. Ms Slack described discrepancies between recommendations and real-life practices. While guidelines suggest that tapering should only be undertaken in patients exhibiting sustained remission with imaging also displaying low disease activity, treatment decisions ultimately lie with the patient, and she noted that patients do often taper their own medication without prior HCP engagement. HCP should be wary, therefore, that patients may look to meet their own expectations without a discussion with their treatment team. Equally, HCP who openly and proactively discuss treatment preferences with patients can foster increased adherence rates and better outcomes.

Conclusion

The introduction of efficacious biologic treatments has revolutionised therapeutic pathways for the treatment of RA and, accompanying their more widespread use, there has been increased patient expectation for treatment success. More cost-effective biosimilars have the potential to reduce the financial burden on health economies and to allow effective biologic therapies to be introduced earlier in treatment pathways, but challenges may be involved relating to patient expectations. Looking forward, the introduction of biosimilars may spark discussion among policymakers and medical societies and serve as an opportunity to recommend earlier use of biologics to best exploit the vital therapeutic window of opportunity. The possible place of TDM as a tool to optimise treatment with biologics might aid in sustaining responses and making informed treatment selection decisions, while also reducing financial burden. The introduction of biosimilars offers optimisation of RA treatment, and the availability of more effective therapies increases the likelihood of patients finding a treatment that suits their lifestyle and meets their expectations.

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Considering the Patient Perspective: Challenges Facing Women with Axial Spondyloarthritis and Psoriatic Arthritis

This symposium took place on 13th June 2019 as part of the European League Against Rheumatism (EULAR) Congress 2019 in Madrid, Spain

Chairpeople: Prof Irene van der Horst-Bruinsma[1]

Speakers: Prof Helena Marzo-Ortega,[2] Dr Laura Coates[3]

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Meeting Summary

This symposium took place during the 2019 European League Against Rheumatism (EULAR) congress in Madrid, Spain, and focussed on the unique challenges facing women with axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA), highlighting differences in diagnosis, disease course, and treatment response between men and women.

Compared to men, women have a longer delay to axSpA diagnosis, higher disease activity, lower quality of life, and experience more fatigue, peripheral involvement, and functional impairment, despite less radiological damage and a lower treatment response to biologicals. In addition, axSpA in general is associated with depression, anxiety, reduced work productivity, and an increased risk of adverse pregnancy outcomes.

Women with PsA typically present with a higher number of involved joints than men, poorer patient-reported outcomes, and a lower quality of life. They also report higher disability scores, more fatigue, a higher prevalence of depression, and often delay or abandon decisions to start a family or to breastfeed their infants. Although a treat-to-target approach is endorsed by both EULAR and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) guidelines

for the management of PsA, minimal disease activity (MDA) is less frequently achieved by women compared to men.

Biologic anti-TNF drugs are efficacious in both SpA and PsA. However, during pregnancy and breastfeeding, most anti-inflammatory biologics used for the management of PsA and SpA are not recommended because of the risk of drug transfer across the placenta to the fetus or via the breastmilk to the infant. Exceptions are the TNF inhibitors adalimumab and certolizumab pegol, a PEGylated Fab' fragment of a humanised monoclonal antibody, for which use in pregnancy and breastfeeding has been documented by clinical and registry data.

In conclusion, efficacious treatment strategies do exist that allow women with axSpA or PsA to achieve satisfactory disease control, also during pregnancy and when breastfeeding.

Sex and Gender Differences in Axial Spondyloarthritis and Psoriatic Arthritis

Professor Irene van der Horst-Bruinsma

Although gender is defined by psychological and social differences between men and women, and sex is defined by biological parameters based on genetics, anatomy, and physiology,[1] the term 'gender' will be used throughout this symposium report to represent both sex and gender differences. In humans, gender is genetically determined by the X and Y chromosomes, and although the male and female versions of the human genome differ in only a limited number of genes located on either, differences in gene expression between men and women are distributed across the entire genome and not only focussed exclusively on the X and Y chromosomes.[2]

Additionally, differences between men and women are often not considered in drug development, as drugs are predominantly tested in healthy male volunteers, with no correction of dosages for body weight and gender, or correction for gender in post marketing studies (Figure 1).[3] Other differences between men and women that may impact the effectiveness and safety of drugs in women are that women have smaller kidneys with a lower glomerular filtration rate, which leads to a lower rate of drug elimination; they have a smaller liver, which leads to lower first pass drug metabolism; have a higher stomach pH; a longer gut transit time; and a higher body fat percentage.[3] Furthermore, due to safety concerns, most drugs are not tested in pregnant or breastfeeding women,[3,4] thus leaving a degree of uncertainty regarding whether approved drugs are indeed safe for pregnant or breastfeeding women.

Figure 1: Drug development and sex.

Adapted from Tannenbaum et al.[3]

Gender differences have also been observed in male and female immunological responses to foreign and self-antigens, and these differences contribute to variations in the incidence of autoimmune diseases seen in men and women.[2] Women are generally more frequently affected by autoimmune diseases than men, and this may be explained by gender differences in immunology, physiology, reproductive function, or sex hormones.[2,5]

axSpA and PsA are two related autoimmune diseases that are associated with elevated levels of the pro-inflammatory cytokine TNF-alpha.[6] SpA comprises a group of chronic inflammatory diseases that share common pathophysiological, genetic, and clinical features, including inflammation of one or both of the sacroiliac joints (sacroiliitis). Depending on clinical manifestation, SpA can be classified as either axial or peripheral (non-axial; non-axSpA), and ankylosing spondylitis (AS) is viewed as a more advanced or severe form of axSpA.[7] PsA is a heterogeneous condition that in addition to skin and nail disease (psoriasis), may manifest as arthritis (joint inflammation), enthesitis (inflammation of the sites where tendons or ligaments insert into the bone), dactylitis (inflammation of the fingers), or axial (spinal) involvement.[8]

A study using data pooled from four clinical trials found that, compared with men, women have a higher disease burden and less improvement in Ankylosing Spondylitis Disease Activity Score (ASDAS) after 12 weeks of TNF inhibitor treatment.[9] Furthermore, women appear to have a lower response rate to TNF inhibitor treatment compared with men (1-year follow-up: women: 43%, men: 62%; 2-year follow-up: women: 46%, men: 59%).[10,11] Additionally, women with axSpA also stay on the same drug for a shorter time period than men (33.4 versus 44.9 months) before discontinuing or switching treatment, mainly because of inefficacy.[12]

Several anti-inflammatory biologic drugs targeting TNF, such as the engineered monoclonal antibodies adalimumab, certolizumab pegol, infliximab, and golimumab, and the fusion protein etanercept, are approved for the treatment of autoimmune diseases such as axSpA and PsA.[13] However, gender specific differences in the diagnosis, disease progression, and treatment options for axSpA and PsA need to be considered in order to achieve optimal disease control for both men and women.

The aim of this symposium was to highlight the unique challenges facing women diagnosed with axSpA and PsA, and to discuss how emerging data may impact on the clinical management of female axSpA and PsA patients.

Expert Discussion: Axial Spondyloarthritis

Associate Professor Helena Marzo-Ortega

axSpA is not a male specific disease. Radiographic axSpA (r-axSpA/AS) is more common in men than in women (67% versus 33%), whereas the reverse has been reported for non-radiographic axSpA (nr-axSpA) (67% in women; 33% in men).[14] In nr-axSpA, in contrast to r-axSpA, substantial erosive damage to the sacroiliac joints has not yet occurred.[15]

Compared to males, female axSpA patients also have a lower ASAS-criteria treatment response and lower treatment improvement, more active axSpA disease, higher disease severity, and a lower quality of life.[16-19] However, radiological damage and disease progression appear to be worse in men, and men are also younger at diagnosis (men: 27 years; women: 30 years; p=0.02), and have a shorter delay to diagnosis.[20,21] Although this diagnostic delay in general appears to be shrinking year-on-year, women still wait significantly longer for diagnosis than men (women: 8.8 years; men: 6.5 years; p=0.01).[22,23] Interestingly, a recent report suggests that concomitant noninfectious acute anterior uveitis and chronic back pain are more common in patients with axSpA, which may help speed up the diagnosis of axSpA in both men and women.[24] Pregnancy and childbirth, on the other hand, add additional complexity to the diagnosis of axSpA, as post-partum back pain may result in a false positive diagnosis of axSpA.[20]

Whereas men meet modified New York disease activity criteria more often, women with early axSpA have greater subjective disease activity, and tend to have more widespread pain, which may contribute to the delay to diagnosis.

Additionally, women with definite sacroiliitis may experience more fatigue, peripheral involvement, and have a more relevant family history than men, and may also have more functional impairment, despite less radiological damage.[20,25-27]

Being affected by a potentially serious health problem may have a significant impact on mental wellbeing, and the process from initial diagnosis to acceptance of a disease, its symptoms, and treatment options has been described as a form of grieving process. During the pre-diagnosis phase, when symptoms are first recognised, patients may react with shock, denial, and frustration. In the time period following the diagnosis, low mood, and depression may slowly be replaced by engagement with the diagnosis and the disease and learning how to adjust to the new reality of living with a disease diagnosis. Once the patient comes to terms with this new situation, a new equilibrium is established.[28]

axSpA has a recognised negative impact on mental wellbeing, which may manifest as depression and anxiety. The mental health impact of axSpA appears to be correlated with disease activity, and seems to affect men and women equally.[29-32] Patients with both r-axSpA and nr-axSpA seem to experience similarly reduced work productivity, and a study investigating work disability among male r-axSpA patients showed that almost half (45%) of patients switched to a less physically demanding job, and a quarter (24%) retired early at a mean age of 36 years.[33,34] Nevertheless, non-biologic and biologic treatments are available and, in this respect, a British registry study and meta-analysis found that there is consistent evidence that treatment with biological therapy, compared with non-biological treatment regimens, significantly improves work productivity and activity impairment in people with axSpA.[35]

The C-axSpAnd trial, which investigated the effect of the addition of the anti-TNF biologic certolizumab pegol to non-biologic background medication, found that adding certolizumab pegol to non-biologic background medication is superior to adding placebo in patients with active nr-axSpA.[36] Interestingly, a recent post-hoc analysis of disease outcomes in C-axSpAnd trial patients, stratified by symptom duration, found that patients with shorter symptom duration showed greater improvements in signs and symptoms of nr-axSpA.[37]

Pregnancy is an important topic for women, and rheumatologists need to bring up the subject and have a frank conversation with women diagnosed with axSpA about disease control, which drugs are compatible with pregnancy and the post-partum period, and what will happen during delivery. There are risks for adverse pregnancy outcomes in axSpA, and disease activity does matter.[38] No ameliorating effect on axSpA disease activity has been reported because of pregnancy, and 60–80% of pregnant patients become symptomatic again, with increased pain and morning stiffness starting approximately at Week 20.[39-41] Furthermore, active disease (ASDAS-C-reactive protein >2.1) has been reported in 78% of axSpA patients during pregnancy, most commonly in the second trimester.[38] Women with axSpA also seem to have increased risk for gestational diabetes, pre-eclampsia, infection, preterm premature rupture of the membranes, small for gestational age infants, and preterm delivery.[38] Active disease is a predictor of preterm delivery, and more preterm births have been reported in women with axSpA compared with population controls, especially in women not exposed to any medications.[42]

Both biologic and non-biologic anti-inflammatory drugs are used in axSpA, but not all drug types are appropriate during pregnancy. Nonsteroidal anti-inflammatory drugs (NSAID) may be used in pregnancy, but COX-2 selective NSAID are not recommended.[43] COX-1/2 enzymes are involved in ovulation and implantation, and COX-1/2 inhibitor NSAID, with the exception of paracetamol, may be associated with an increased risk of miscarriage.[44] Furthermore, NSAID are not recommended in the third trimester because of an increased risk of patent ductus arteriosus closure failure in the infant.[45]

A major concern with the use of biologics in pregnancy is placental transfer from the mother to the fetus. Maternal antibodies are typically transferred across the placenta to the fetal circulation through a mechanism known as transcytosis, and involves binding of the antibody Fc domain to Fc receptors situated on the surface of syncytiotrophoblast cells of the placenta.[46] This mechanistic dependency on the presence of an antibody Fc domain determines

how effectively antibodies are transferred across the placenta from the mother to the fetus, and may be important for how pregnant women are treated with anti-inflammatory biologics. The biologics adalimumab, etanercept, golimumab, infliximab, ixekizumab, secukinumab, and ustekinumab all contain antibody Fc domains, and adalimumab, etanercept, golimumab, and infliximab are known to cross the placenta.[47-54] No data is available on transplacental transport of ixekizumab, secukinumab, and ustekinumab.[55-61] Certolizumab pegol, on the other hand, is a PEGylated Fab' fragment of a humanised anti-TNF monoclonal antibody that does not contain an Fc domain.[62] As a consequence, the prospective pharmacokinetics study CRIB demonstrated minimal-to-no placental transfer of certolizumab pegol during pregnancy. Of the 14 infants that completed the study, 13 had no quantifiable levels of certolizumab pegol at birth (<0.032 µg/mL), and 1 infant had a minimal certolizumab pegol level (0.042 µg/mL; infant/mother plasma ratio: 0.09%).[63] The European Medicines Agency's (EMA) product labels state that certolizumab pegol should only be used during pregnancy if clinically needed, and that adalimumab, etanercept, and infliximab should only be used during pregnancy if clearly needed. Golimumab, ixekizumab, secukinumab, and ustekinumab are not recommended for use during pregnancy.[55-63]

The biologics adalimumab, certolizumab pegol, and etanercept are excreted into breastmilk, whereas no data is available for infliximab, golimumab, ixekizumab, secukinumab, or ustekinumab.[55-63] The prospective pharmacokinetic study CRADLE demonstrated that the relative infant dose of certolizumab pegol transferred from plasma to breast milk is 0.15% of the maternal dose. To put these results in context, a relative infant certolizumab pegol dose below 10.00% of the maternal dose is considered unlikely to be of clinical concern, which supports continuation of certolizumab pegol treatment during breastfeeding.[64] EMA label Information concludes that certolizumab pegol and adalimumab can be used during breastfeeding, whereas etanercept, golimumab, infliximab, ixekizumab, secukinumab, and ustekinumab are not recommended.[55-63]

Patients and physicians often have different perspectives for the management of axSpA. Physicians may emphasise outcome measures, treatment options, and disease progression, whereas patients may put more emphasis on impact on work, friends, and family.

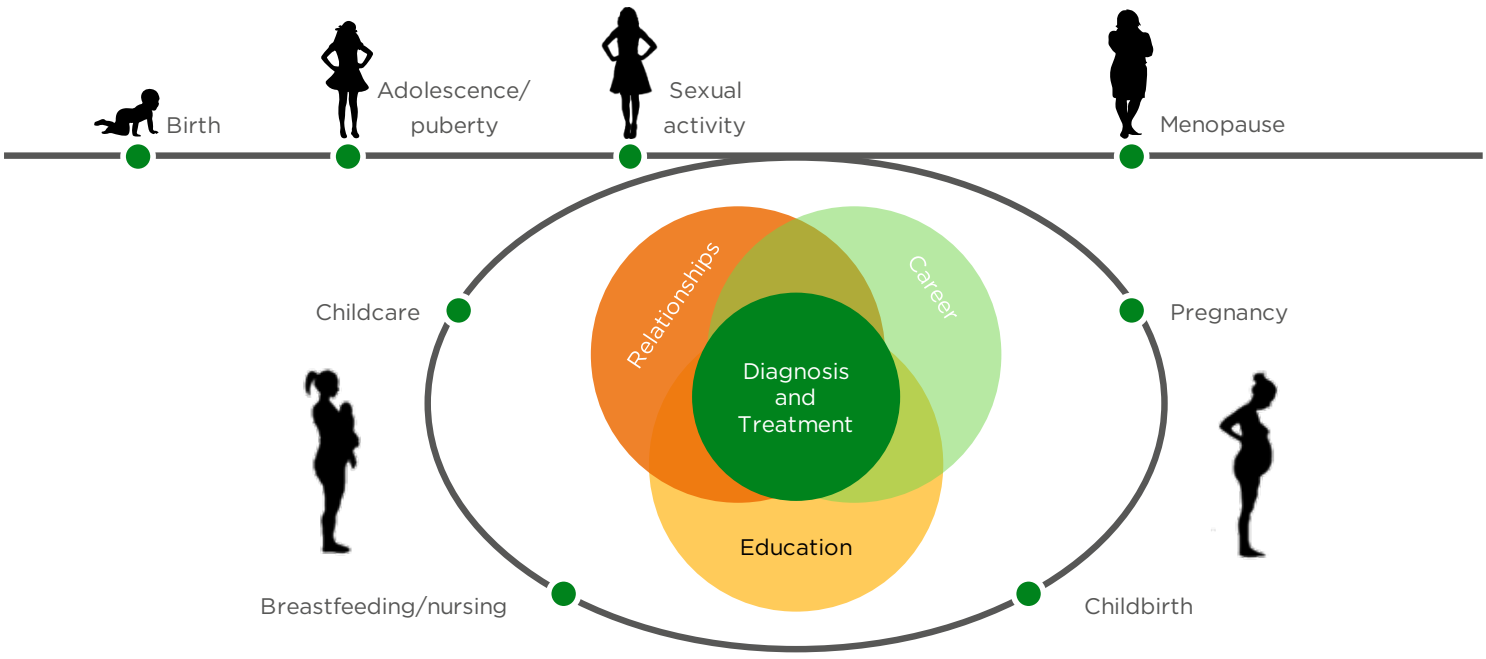

Figure 2: A woman's life journey is not linear, and may be interrupted by multiple cycles of pregnancy, childbirth, breastfeeding, and childcare, which may require therapy realignment at each stage.

Rheumatologists therefore need to see beyond clinical signs and recognise that different people have different needs, and that effective patient-physician communication is needed in order to optimise therapy.[65] A woman's life journey is not linear, and may be interrupted by multiple cycles of pregnancy, childbirth, breastfeeding, and childcare, which may require therapy realignment at each stage (Figure 2).[66]

To illustrate an individual SpA patient's life journey, the story of Hannah, an AS patient, was presented to the symposium audience. At the age of 18, Hannah first presented with back pain and, based on sacroiliac joint fusions on X-rays, was diagnosed with AS only 5 years later. In her 20s, Hannah began using a walking stick, and found that even going out for dinner was a challenge. As Hannah experienced more pain in her hands and knees, she was eventually put on a biologic which dramatically changed her life for the better. Hannah's case related how she stopped treatment when pregnant, and how challenging disease management and motherhood can be. Hannah's case also illustrated the lack of understanding of her work environment and the importance of getting the whole care team, including her obstetrician and midwife, involved with the treatment plan.

Expert Discussion: Psoriatic Arthritis

Doctor Laura Coates

PsA symptoms overlap with both psoriasis and rheumatoid arthritis (RA), and although joint inflammation is present in both RA and PsA, it takes longer to diagnose PsA (28.6 weeks) compared with RA (21.6 weeks).[67] Women typically present with a polyarticular joint pattern and a higher number of tender and swollen joints than men at diagnosis of PsA, whereas psoriasis and pustulosis palmoplantaris is seen more frequently in men.[68] Patient-reported outcomes and quality of life outcomes are worse in women than in men diagnosed with PsA, and women appear to be more disabled in daily activities and have higher disability scores.[69] Furthermore, women also have different pain perception compared with men, and report a higher fatigue severity score.[61] A Dutch study found that women with early PsA presented with higher SF-36 mental component and physical component summaries compared to a reference population.[70] Additionally, women with PsA exhibit higher impact of disease in multiple domains, including pain, skin, fatigue, work, function, discomfort, sleep, anxiety, coping, embarrassment, participation, and depression.[71] In 2015, depressive and anxiety disorders were reported in 4.4% and 3.6%, respectively, in the general population.[72]

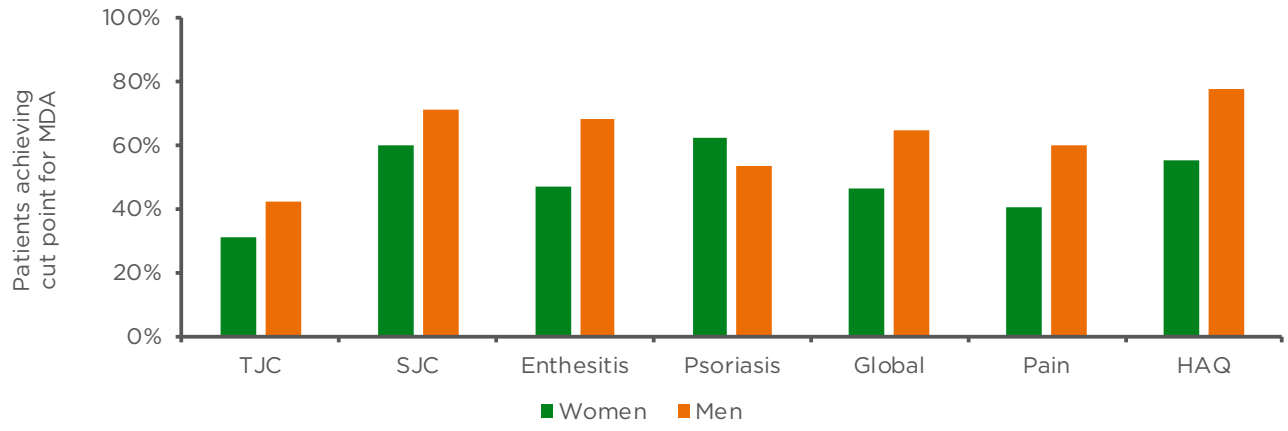

Figure 3: Women with psoriatic arthritis show lower minimal disease activity than men in the TICOPA study.

HAQ: health assessment questionnaire; MDA: minimal disease activity; SJC: swollen joint count; TJC: tender joint count

Adapted from unpublished data, Laura Coates.

In contrast, anxiety, depression, or both, has been reported by 37.0%, 22.0%, and 18.0% of patients with PsA, respectively, and depression in PsA appears to be more common in women (29.0%) than in men (19.0%).[73]

A treat-to-target approach, which aims to reach the target of remission or, alternatively, minimal or low disease activity, through regular monitoring and appropriate adjustment of therapy, is endorsed by both EULAR and GRAPPA guidelines for the management of PsA.[74,75] MDA, defined as meeting five out of seven set criteria,[76] is generally achieved by biologic therapies in approximately 40.0% of PsA patients after 1 year of therapy.[77] In the TICOPA study, which evaluated tight disease control versus standard care in early PsA, fewer women achieved MDA than men in response to either standard care (men: 22.0%; women: 12.0%) or tight control (men: 35.0%; women: 23.0%) (Coates et al., unpublished data), with men outperforming women at all seven MDA domains (Figure 3).

Changes have also been observed in PsA disease activity, particularly for tender joint counts and C-reactive protein levels, which are elevated in women compared with men at both baseline and after 5 years of follow-up. Additionally, women have a less favourable response to therapy compared with men, lower rates of MDA (women: 33.0%; men: 50.0%), and remission (women: 13.0%; men: 25.0%) after 5 years of follow-up, and require a longer time to achieve MDA from diagnosis .[68,78]

Women of childbearing age with PsA face many hurdles around pregnancy and often delay or abandon decisions to start a family and to breastfeed their infants.[79] Key reasons are due to misconceptions regarding their ability to conceive and carry a baby to term, fear of passing the disease to the newborn, and a lack of information and physician support.[80,81] Women of childbearing age with a psoriatic disease such as PsA require adequate treatment, but despite the availability of effective therapies, their use is suboptimal in this population.[79]

Insight into an individual PsA patient's experience was provided through the experience of Sophie, who was diagnosed with PsA 7–8 years after initially presenting to primary care with knee monoarthritis. When upon diagnosis she was started on methotrexate, she was told by her consultant that she would not be able to have any more children. Sophie's psoriasis and arthritis improved during treatment, and on her own she started researching treatment options for PsA patients that are compatible with pregnancy. Together with her physician, Sophie decided on the most suitable treatment option for her considering her current priorities. As such, she is reassured that if she wants another child, she can consult with her physician and come up with a joint treatment plan that works for her and that will support her through both pregnancy and breastfeeding.

Conclusion

axSpA and PsA affect men and women differently. Compared with men, women experience longer delay to diagnosis, lower treatment response and shorter drug survival, experience more pain, carry a larger mental health burden, and experience a reduced quality of life. Women also face unique challenges associated with finding suitable anti-inflammatory treatment options that are compatible with pregnancy and breastfeeding, stressing the need for appropriate physician-patient communication and joint decision making.

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Metacognition in Rheumatoid Arthritis: Thinking About Our Thinking in Rheumatoid Arthritis Management

This satellite symposium took place on 12th June 2019 as part of the European League Against Rheumatism (EULAR) Congress in Madrid, Spain

Chairperson: Andrea Rubbert-Roth[1]

Speakers: Andrea Rubbert-Roth,[1] John Weinman,[2] Daniel Aletaha[3]

1. Kantonsspital, St. Gallen, Switzerland
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3. Medical University of Vienna, Vienna, Austria

Disclosure: Prof Rubbert-Roth has received consultancy fees and honoraria for lectures from AbbVie, BMS, Celgene, Lilly, MSD, Novartis, Roche, Sanofi Genzyme, Regeneron, and UCB. Prof Weinman has received a PhD research grant from Merck and serves on the Behavioural Science Advisory Board for Sanofi. He has presented talks for AbbVie, Bayer, Chiesi, Boehringer Ingelheim, Roche, Merck, Sanofi Genzyme, and Regeneron. Prof Aletaha has received speaker and/or consultancy fees from AbbVie, Amgen, Celgene, Lilly, Medac, Merck, Novartis, Pfizer, Roche, Sandoz, Sanofi Genzyme, and Regeneron. He has also received grants from AbbVie, Novartis, and Roche. Prof Leonard Calabrese was involved in the development of the symposium and in reviewing this article. He has received consultancy fees from Amgen AbbVie, BMS, Genentech, Janssen, UCB, Horizon, Sanofi Genzyme, Crescendo, GSK, Pfizer, Lilly, and Gilead. He has also received speaker fees for non-branded activities from AbbVie, BMS, Genentech, Janssen, Horizon, Sanofi Genzyme, Regeneron, Lilly, and Celgene.

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Meeting Summary

Metacognition is thinking about thinking, knowing about knowing, and being aware of your own awareness. It refers to the processes used to plan, monitor, and assess our own understanding and performance. By applying this metacognition concept and thinking critically about current beliefs and practices in the management of rheumatoid arthritis (RA), this symposium aimed to help rheumatologists think about how to positively impact patient care. Prof Andrea Rubbert-Roth introduced the meeting by looking at current approaches to the management and treatment of RA and the disconnect between the treatment goals of physicians and patients. Prof John Weinman provided an overview of the causes and extent of non-adherence, focussing on the role of patient beliefs and the use of consultations to facilitate better adherence. In the third presentation, Prof Daniel Aletaha applied the concept of 'the ideal' versus 'the norm' to three important areas in the management

of RA: how we define remission, how we measure remission, and the minimally clinically important difference (MCID) in treatment outcomes as perceived by the patient. Prof Rubbert-Roth followed up with a review of the data on cycling or switching between different classes of biologic treatment and the use of patient characteristics and, eventually, biomarkers to guide the preference of clinicians for drugs targeting tumour necrosis factor (TNF) or other targets with overlapping but distinct signalling pathways, such as IL-6. Finally, Prof Weinman discussed the holistic care and treatment of patients with RA, emphasising the need for an empathic and collaborative approach to patient care.

Is it Possible to Achieve Better Disease Control in Rheumatoid Arthritis?

Professor Andrea Rubbert-Roth on behalf of Professor Leonard Calabrese

Since the 1990s, outcomes for patients with RA have steadily improved over time, with the treatment target for patients evolving from symptomatic relief, to prevention of damage and disability, and finally towards disease remission.[1,2] These improvements in outcomes have occurred alongside advances in therapy and collaborative goal setting between rheumatologist and patient. Indeed, the rheumatology field may seem very fortunate, with a broad range of treatments and an established treat-to-target strategy that has transformed clinical remission from a long shot into an achievable target. In reality, only 30–40% of patients achieve clinical remission and for many patients their disease remains uncontrolled.[3] In patients who respond inadequately to methotrexate and/or a first-line TNF inhibitor (TNFi), residual inflammation remains an important issue irrespective of subsequent treatment and represents a major unmet need (Figure 1).[1]

The therapeutic options for RA will continue to expand, with cytokine and signal transduction targets remaining the predominant focus of drug development,[4] but what else can rheumatologists do with what they already have? Could thinking differently about current thinking and practices in RA management offer another route to achieving better disease control, building upon past successes in managing this disease? Prof Rubbert-Roth believes a good starting point is to examine the disconnect between patient and physician perceptions of treatment goals and exploring ways to overcome this in clinical practice.

Physicians have been taught that by achieving disease remission they can ultimately stop the development of radiographic progression, reduce physical disability, and have a positive impact on mortality.[5-7] However, the most important aspects of care from the patient's perspective are control of pain and fatigue and maintenance of physical function and health-related quality of life.[6-10]

During the course of a typical day, a patient with RA may experience a range of negative aspects of their disease that physicians may not necessarily be aware of, or may not directly address with the patient; for example, many patients with RA experience anxiety and depression, reduced sexual functioning, and may be limited in their work and social participation.[6,11,12] The disconnect is clear when comparing the factors that drive patients' and physicians' global assessment scores. From the patient side, pain is the principal driving factor, whereas physicians may place more emphasis on number of swollen joints.[13] This presents a scenario wherein the disease is well controlled in terms of inflammation, satisfying the physician, but the patient may still have residual pain and fatigue, and not be completely satisfied with their care. This amounts to an unmet medical need from the patient's perspective.

In the context of treatment goals in RA, patients want their pain to be completely resolved, not just reduced, and to be able to do the activities they enjoy.[14] Good QoL is paramount. Physicians, on the other hand, aim for no or very low levels of inflammation, no accrual of joint destruction, and no drug-related side effects, with QoL as a secondary concern.[15] This suggests that good communication and greater collaboration between patients and physicians could positively impact the management of RA. Treating an inflammation-based target is undoubtedly important, but not good enough.[15-18] A dual target strategy, a treat-to-target approach that takes into account of collaborative goal setting

between physicians and patient, offers a way forward, in which the patient's personal goals are also targeted through shared decision-making.[19] For example, patient-perceived remission may include such goals as absence or reduction of symptoms, decreased daily impact of their condition, and a feeling of returning to normal.[20] Prof Rubbert-Roth concluded by identifying gaps where changes could be made to positively impact the care of patients living with RA. The majority of these focussed on the patient physician interaction, emphasising the importance of collaboration, empathic communication, shared decision-making, identifying and managing patient concerns, considering their beliefs and adherence, and taking a whole-patient approach to their care. Through these collective actions, rheumatologists can provide a truly optimal, tailored treatment that meets therapeutic targets, including comorbidities and patient-reported outcomes (PRO).[15]

The Role of Patient Beliefs in Rheumatoid Arthritis Adherence and Therapy Optimisation

Professor John Weinman

Adherence has long been discussed as a public health issue but its impact is not routinely assessed in clinical practice and is often underestimated.[21,22] A 2018 working paper published by the Organisation for Economic Co-operation and Development (OECD) concluded that poor adherence is "a major public health problem", contributing to 200,000 early deaths annually in Europe, with an estimated cost of €125 billion.[22]

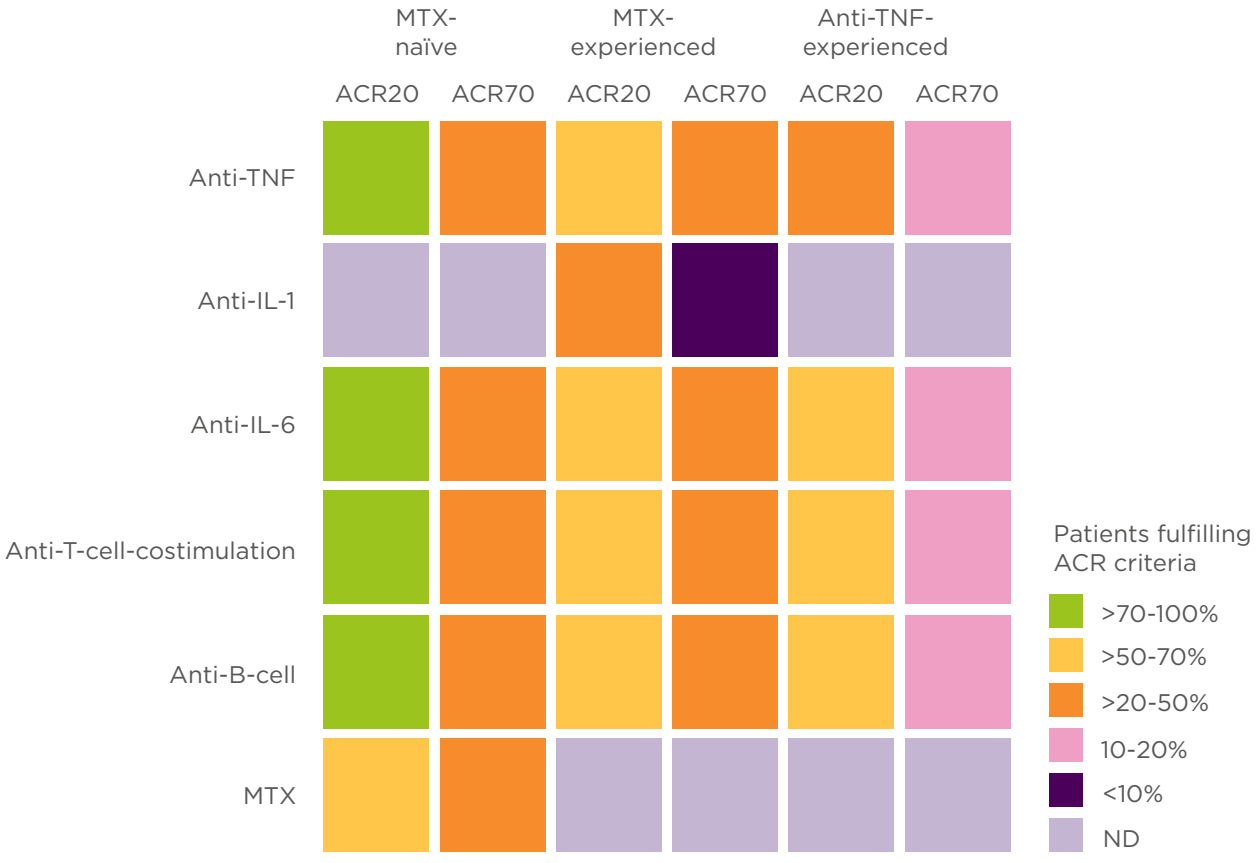

Figure 1: Patients fulfilling ACR criteria by prior RA treatment

Adapted with permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Nat Rev Rheumatol. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges, Smolen JS and Aletaha D, Copyright (2015).[1]

ACR: American College of Rheumatology; MTX: methotrexate; ND: not done; TNF: tumour necrosis factor.

Reasons for this include a lack of awareness among practicing physicians and unwillingness to take ownership of the problem.[22,23]

Adherence can be separated into three distinct phases: uptake, implementation (how patients integrate the treatment into their lives), and persistence (how long patients stay on treatment).[24] In patients with chronic metabolic diseases, up to 31% never start their prescribed treatment ('primary non-adherence'). Of those who do start treatment, only 50–70% are regularly adherent and less than half persist on treatment for 2 years.[22] Reported rates of non-adherence vary considerably in RA, partly due to differences in study methodology.[25] In a systematic review of 52 studies, as many as two-thirds of patients stopped biologic treatment within 1 year, with overall adherence of 41–81%.[25] Evidence shows that the impact of non-adherence in RA manifests not only in increased costs of healthcare but also in a clear effect on remission, likely falling short of patients' personal goals.[26,27] Non-adherent patients are only half as likely to achieve remission, and take twice as long, as patients who take treatment as directed.[27]

To determine the reasons for non-adherence, it is necessary to look not only at the drivers of patient behaviour, but also at the contribution of physicians and healthcare systems. A convenient way to look at drivers of patient behaviour is to apply a Capability, Opportunity and Motivation (COM-B) model.[28,29] Each of the three components are important in driving patient behaviour in RA, but perhaps the most influential are the patient's own perceptions. These can be categorised as perceptions of illness (i.e., patients' beliefs about the nature, cause, consequences, timeline and cure/control of their condition); perceptions of treatment (i.e., do they doubt its necessity and/or do they have concerns about potential adverse effects?); and beliefs about self-efficacy (i.e., are they confident in their ability to continue taking the treatment over time?).[28] Studies of patients with chronic diseases, including RA, clearly show that patients who doubt the necessity of day-to-day treatment and concerns about safety are least likely to adhere to treatment.[29-32] Taken together, the evidence shows that not only can beliefs vary enormously between patients, but they can also vary within the same patient over time as the pattern of treatment and treatment response changes. Prof Weinman emphasised the importance of not adopting a 'one size fits all' approach to interventions to improve adherence, but instead working to identify the issues that apply to each individual patient and then using personalised behaviour change interventions.[33]

From the physician's perspective, an initial default thinking when a patient is not responding to a certain treatment is to increase the dose or switch to an alternative. It is unusual for physicians to check whether the patient has actually been taking their treatment as directed.[22] Even when the question is asked, it is often asked in a way that patients feel obliged to give a misleading answer. Research also shows that adherence is not easily intuited; in one study, the physician's beliefs about which of their patients are non-adherent were no more accurate than chance.[34] There is a clear need for tools and training to improve open discussion between physicians and patients on individual adherence issues and how to manage these collaboratively. Physicians should periodically check patients' understanding of treatment, using patient-friendly language, and take steps to improve this if needed. Steps may include providing a clear rationale for the necessity of the treatment, eliciting and responding to patient concerns, agreeing on a practical plan for how, where and when to take treatment, and identifying potential barriers.[31]

The Ideal versus The Norm: What Does Minimally Important Difference Mean and Why is This Important in Management of Rheumatoid Arthritis Today?

Professor Daniel Aletaha

Prof Aletaha applied the concept of 'the ideal' versus 'the norm' to three important areas in the management of RA. In the context of clinical remission, the question today is not necessarily whether remission is too ambitious but whether it is not ambitious enough. Could subclinical remission, also known as imaging remission, become the new ideal?[15] Randomised studies exploring whether structural and functional outcomes are significantly superior in patients who go beyond clinical remission to achieve subclinical remission have so far yielded negative

results.[35-37] In the ARCTIC study, ultrasound tight control (defined as clinical remission and no ultrasound power Doppler signal) was not significantly superior to conventional tight control for the composite primary endpoint of disease activity score (DAS) <1.6, no swollen joints and non-progression of radiographic joint damage at 16 and 24 months.[35] Similarly, the TaSER trial in newly diagnosed patients with RA or undifferentiated arthritis randomised to clinical remission or imaging remission (defined as total power Doppler joint count ≤1) found no significant difference between the two groups for any clinical outcome.[36]

In the third study, IMAGINE-RA, imaging remission (defined as no evidence of bone marrow oedema on magnetic resonance imaging [MRI]) also failed to demonstrate superiority over conventional tight control on the primary endpoints of remission and radiographic non-progression. However, statistically significant differences were reported for four of the secondary outcomes (American College of Rheumatology-European League Against Rheumatism [ACR-EULAR] Boolean remission, swollen joint count, patient global visual analogue scale assessment, and change in Health Assessment Questionnaire [HAQ] score) after 2 years of treatment.[37] Overall, while acknowledging that treating to an imaging remission target may be of benefit in some patients, the current evidence does not support the use of more intensive monitoring and therapy in addition to conventional tight control. On a practical level, repeat MRI scans may not be feasible in clinical practice.

Prof Aletaha also explored 'the ideal' versus 'the norm' in terms of how we measure remission. Clinical studies commonly measure remission using DAS in 28 joints (DAS28) based on C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), but neither outcome is recommended by ACR-EULAR due to lack of specificity.[38] Even with adjusted cutpoints, around half of patients in remission according to DAS28-ESR (≤2.2) and around 30% of patients in remission according to DAS28-CRP (≤1.9) had at least one swollen joint, compared with only 10% of patients when remission was based on the ACR-EULAR recommended Clinical Disease Activity Index (CDAI).[39] The problem with DAS28 remission is not the cutpoints but the strong weighting given to the acute phase response. This is clearly shown when comparing DAS28 remission responses with cytokine-based versus non-cytokine-based biologics. In the ATTAIN and REFLEX trials of the non-cytokine-based biologics abatacept and rituximab, respectively, DAS28 remission rates were similar to AC70 response rates, whereas in the RADIATE trial of the IL-6 receptor inhibitor tocilizumab, more patients achieved DAS28 remission than achieved an ACR50 response.[40-42] Thus, DAS28 remission rates depend not only on efficacy but also on type of intervention.

The Boolean criteria recommended by ACR-EULAR are not infallible either. An estimated 61% of patients who are 'near-misses' for clinical remission (that is, patients who fulfil only three of the four ACR-EULAR Boolean criteria) fail to reach remission because of high patient global assessment (PtGA) scores. Pain is highly predictive of near-misses related to PtGA, and this is true regardless of whether the pain is related to inflammation or not.[43] Given that there is a clear link between non-inflammatory pain and depression – the leading comorbidity in patients with RA[44] – it is useful to first assess the impact of pain and depression before deciding on a treatment change in patients repeatedly failing objective-established remission criteria.

Finally, Prof Aletaha discussed the concept of the MCID in RA. MCID is typically defined as the smallest difference in a domain score of interest that patients perceive to be beneficial (in the absence of troublesome side effects and excessive cost) that would mandate a change in management.[45,46] It is important to understand that the patient is the anchor of this definition, not least because it necessarily applies that MCID is dependent on baseline disease activity. This dependence has been demonstrated clearly by registry analyses. For example, data from a Norwegian registry identified the MCID cutpoints for improvement of CDAI as 1.8 for low disease activity, 7.3 for medium disease activity, and 17.8 for high disease activity.[47] By comparison, an analysis of the Canadian Early Arthritis Cohort identified the same MCID cutpoints as 1, 6, and 12, respectively.[48]

The MCID is valuable in the context of clinical trials as it offers a useful way to track disease activity from the perspective of the patients, for example when switching to a new biologic. New data from the open-label extension of the

MONARCH trial show that patients switched from adalimumab to sarilumab experienced clinically meaningful improvements in DAS28-CRP, CDAI, and HAQ-DI that generally increased over time (Figure 2).[49] Rheumatologists know from experience that the 3-month timepoint is important; the question is how much change at 3 months do physicians ideally want to see to reassure them about continuing the same therapy or regimen rather than switch to another. A pooled analysis of patient-level data from clinical trials found that achieving a minor response (e.g., ACR20 or a 50% improvement in Simplified Disease Activity Index [SDAI 50%]) at 3 months is associated with very low negative likelihood ratios for achieving SDAI low disease activity or remission at 6 months.[50] On the other hand, rheumatologists can be confident in continuing the same therapy if the patient has a major response (e.g., ACR70, SDAI 85%, or EULAR good response) at 3 months.

Changes in Daily Rheumatoid Arthritis Practice: Dealing with Loss versus Gain in Switching versus Cycling

Professor Andrea Rubbert-Roth

TNFi remain the most commonly used biologics in the management of patients with RA, supported by extensive experience and a wealth of data on long-term safety, cardiovascular benefits, and broad efficacy for spondyloarthropathies and other inflammatory joint diseases.

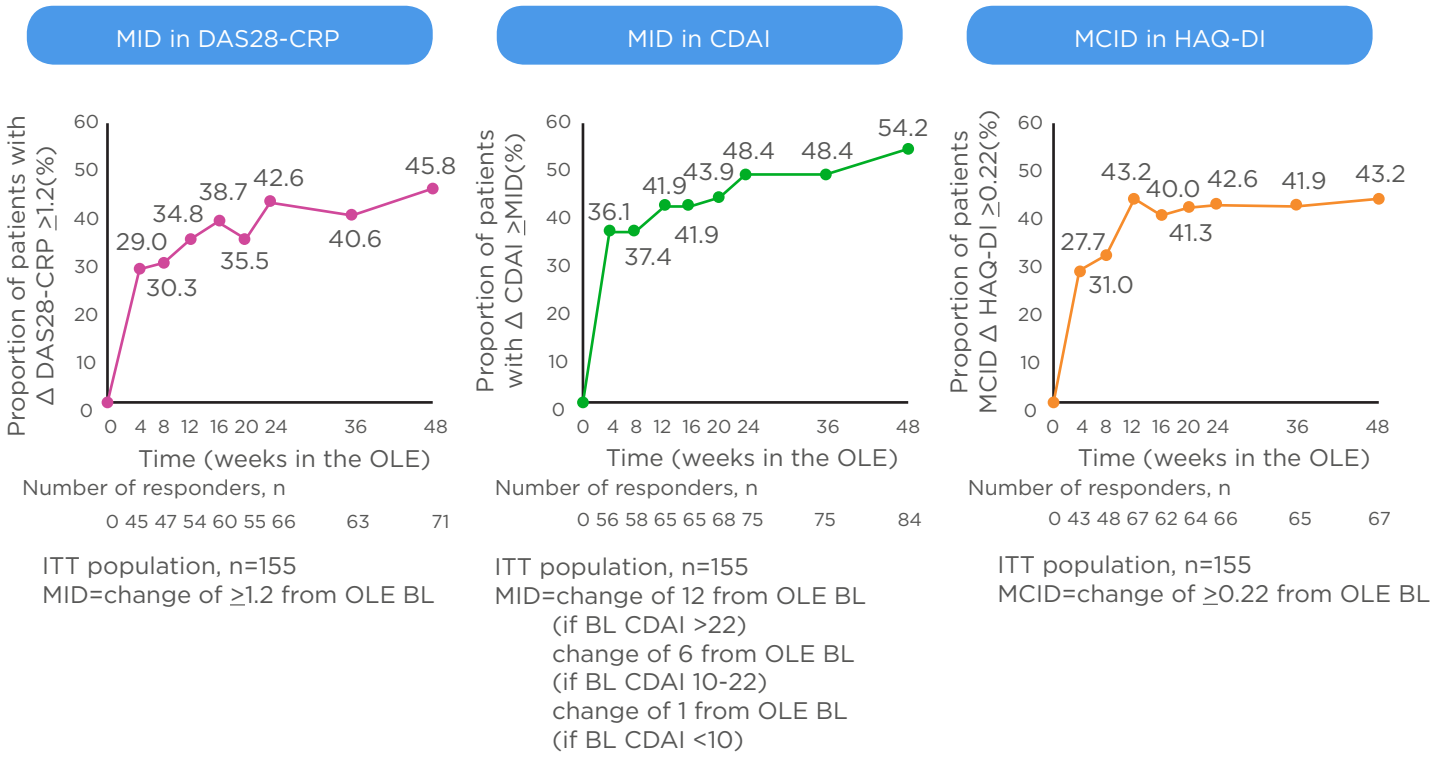

Figure 2: Minimally important difference in switching group from start of open-label extension of the MONARCH study.

BL: baseline; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS: Disease Activity Score; HAQ-DI: Health Assessment Questionnaire – Disability Index; ITT: intent-to-treat; MID: minimally important difference; OLE: open-label extension.

Reproduced with permission from Burmester et al.[49]

Following the failure of a TNFi, EULAR recommends that patients be switched to an alternative drug class with a different mode of action (MOA) or cycled between drugs within the same class to try to mitigate against loss of efficacy.[51] In the absence of biomarkers to truly personalise treatment, rheumatologists are faced with the challenging task of selecting an appropriate strategy that considers all of the clinical factors as well as the patient factors. From the patient perspective, drug selection may be driven by comorbidities and/or need for monotherapy, as well as the patient's beliefs and overall goals. The availability of multiple TNFi and, recently, TNFi biosimilars may also influence prescribing habits.

Cycling to a second TNFi can be efficacious, as demonstrated in the EXXELERATE trial in which primary non-responders to certolizumab pegol were switched to adalimumab, and vice versa, with no washout period.[52] Although the trial was negative, in that it failed to demonstrate superiority of certolizumab pegol to adalimumab, it had important implications for TNFi cycling in clinical practice. It is expected that around 30% of patients receiving their first TNFi will fail to achieve an ACR20 response.[53] In EXXELERATE, a further drop-off in patients responding to treatment was demonstrated in patients who cycled to a second TNFi, with ACR20 response rates of 40–44%.[52]

There is now a wealth of data suggesting that switching to a different MOA may improve clinical outcomes and PRO. EULAR currently recommends switching drug class in patients who experience failure of two successive TNFi,[51] but should clinicians be switching sooner? The Rotation or Change trial was designed to answer this question in a head-to-head study in patients randomised to cycling to another TNFi or switching to a non-TNFi biologic. The primary endpoint of EULAR good or moderate response at Week 24 was met by 69% of patients who switched and 52% of patients who cycled (p=0.004). At Week 52, switching was statistically significantly more effective than cycling across all secondary efficacy endpoints (EULAR good or moderate response, DAS28-ESR remission, and DAS28-ESR low disease activity).[54]

The benefits of switching rather than cycling are supported by results from placebo-controlled trials of non-TNFi biologics, conducted in patients who had an inadequate response or were intolerant to prior TNFi (TNF-IR). In the RA-BEACON study, the JAK1/2 inhibitor baricitinib provided rapid and sustained clinical benefit in TNF-IR patients, with an ACR20 response rate of 46% at Week 24.[55] In comparison, TNF-IR patients treated with the IL-6 inhibitor sarilumab in the TARGET study had an ACR20 response rate of 61% at 24 weeks.[56] Switching to an alternative MOA is also supported by registry data[57,58] and long-term drug retention rates.[54,59] For example, in the Canadian Rhumadata registry, switching to tocilizumab had a 4-year retention rate of 44.3% compared with rates of 27.2–37.1% when cycling through TNFi.[59]

Returning to her earlier point about biomarkers, Prof Rubbert-Roth introduced new data from the MONARCH study indicating that IL-6 may be a potential biomarker for guiding clinical decision-making in patients with RA. High baseline levels of IL-6 were associated with greater improvements in PRO for sarilumab versus adalimumab.[60] Taken together with previously reported evidence of a predictive relationship between baseline levels of IL-6 and greater response to sarilumab,[61] these results suggest an emerging patient profile for responders to treatment. In addition, a post-hoc analysis of data from TARGET and MONARCH shows a more pronounced reduction in glycosylated haemoglobin (HbA1c) with sarilumab versus placebo or adalimumab (Figure 3), irrespective of diabetic status. Notably, HbA1c reductions were greatest with sarilumab monotherapy in patients with high baseline levels of IL-6.[62] Patients on biologic monotherapy are an important group to consider as methotrexate is frequently stopped because of side effects. [63] Clinical trial evidence favours the use of an IL-6 receptor or JAK inhibitor in these patients.[64,65]

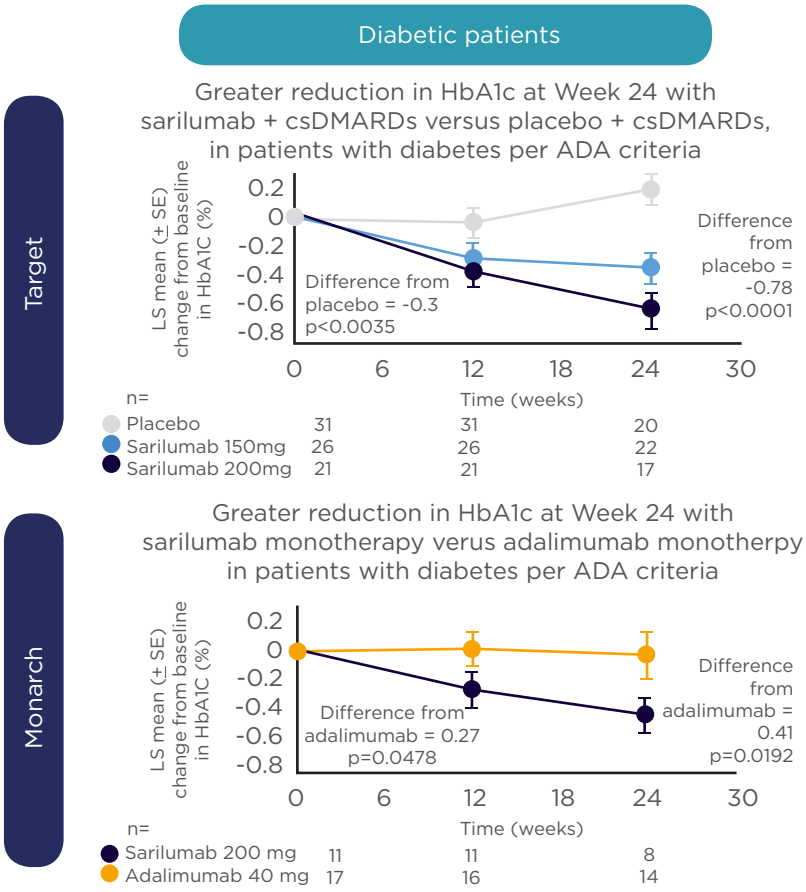

Figure 3: Change from baseline in HbA1c in patients treated with sarilumab versus placebo in the TARGET study and sarilumab versus adalimumab in the MONARCH study.

HbA1c was systematically collected at baseline and Weeks 12 and 24. ADA diagnostic criteria: fasting glucose ≥7 mmol/L or baseline HbA1c ≥6.5%

ADA: American Diabetes Association; csDMARD: conventional synthetic disease-modifying antirheumatic drug; HbA1c: glycated haemoglobin.

Reproduced with permission from Genovese M et al.[62]

Holistic Care of Patients with Rheumatoid Arthritis

Professor John Weinman on behalf of Professor Leonard Calabrese

Prof Weinman argued that empathy should be taken seriously as a core skill that has real value in disease management. Research shows that physicians often miss opportunities to respond empathetically to their patients, leaving them unsatisfied.[66] Qualitative research has shown that patients with RA who feel that no one is listening to them often come away from consultations feeling negatively, not only about their care but also about their ability to self-manage their condition.[67]

The concept of empathy in the context of patient care can be broken down into three core components: developing an understanding of the patient's experiences, concerns, and perspective; having the capacity to communicate this understanding; and showing an intention to help.[68] Recommendations for physicians include being mindful of eye contact, facial expression, posture, affect and tone of voice when speaking to patients, making sure to hear the whole-person perspective, and responding in a way that lets them know they have been heard.[69]

Interventions to increase empathic communication have been successful.[66] Research shows that physicians who incorporate core empathy skills in routine practice feel more personal growth and greater job satisfaction as a result, and are less likely to burn out.[68,70] Patients also benefit, not only in terms of reduced anxiety and greater satisfaction with care – a crucial component of adherence – but also in better clinical outcomes.[71-73] In addition, evidence suggests that the perception of empathic communication as imposing an extra time burden on physicians is false. One study found that use of one empathic statement during outpatient visits can save 1.5–2 minutes per consultation, depending on the medical or surgical nature of the visit.[74]

Further research into empathy in the context of rheumatology is needed to determine the clinical correlates of empathy and the role of empathetic communication in the management of RA. Ideally, the need for empathy skills should be addressed early on during rheumatology training.

Conclusions

Professor Andrea Rubbert-Roth

Despite advances in the treatment of RA only 30–40% of patients achieve remission and for many patients their disease remains uncontrolled.[3] The impact of non-adherence on disease control and patients' personal goals is often underestimated. Non-adherent patients are only half as likely to achieve remission, and take twice as long, as patients who take treatment as directed.[27] Rheumatologists need to be aware of the causes and extent of non-adherence, and to make use of consultations to facilitate informed adherence.[25,28] When considering the patient experience, it is important to note that the MCID is, by definition, the patient perception of improvement and depends on baseline level of disease activity.[45,46] The MCID is therefore a useful way to track disease activity from the patient perspective, for example when switching to a new biologic. In patients with an inadequate response to first TNFi – who may have non-TNF-driven or TNFi-resistant disease – switching to a different MOA may improve outcomes.[53,54] A lack of biomarkers leaves rheumatologists with the challenging task of personalising treatment based on a broad range of factors. Patient characteristics (e.g., comorbidities) may guide physicians' preference for non-TNF-targeted drugs.[60,62] Emerging data suggest that baseline IL-6 levels may have utility as a biomarker for treatment response.[60-62] Clinical trial evidence favours the use of an IL-6 receptor or JAK inhibitor in patients on biologic monotherapy.[64,65] In conclusion, by thinking critically about current beliefs and practices in management of RA and collaborating with patients in an empathetic way to identify and address suboptimal disease control, it is possible to do more to positively impact patient care.

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

This symposium took place on 13th June 2019, as part of the European League Against Rheumatism (EULAR) European Congress of Rheumatology 2019 in Madrid, Spain

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Meeting Summary

The symposium 'Fine-tuning the treatment of PsA: Focus on the IL-23 pathway' took place during the 2019 European League Against Rheumatism (EULAR) Annual Congress in Madrid, Spain. The presentations covered the rationale for targeting IL-23 in psoriatic arthritis (PsA), details of the IL-23 pathway relevant to psoriatic disease, practical implications and consequences of targeting IL-23, and experiences of targeting IL-23 in psoriasis from the dermatologists' perspective.

Dr Stefan Siebert set the scene by outlining the pathophysiology of psoriatic diseases, particularly PsA, describing disease heterogeneity, explaining the role of inflammation, and highlighting the

rationale for targeting the IL-12/23 pathway. He summarised key findings on the IL-12/23 inhibitor ustekinumab in PsA from clinical trials and real-world data available to date.

Delving deeper into the IL-23 pathway, Prof Georg Schett explained the function of IL-23 and its role in inflammatory disease and autoimmunity. After briefly describing the history of the relatively recent discovery of this cytokine, Prof Schett discussed preclinical and clinical studies underlying today's understanding of IL-23 and why it is an appropriate target in PsA.

Multiple biologic or small-molecule treatments for PsA have been investigated in clinical trials. Prof Peter Taylor discussed the practical implications of targeting IL-23 and provided more details about the specific effects of targeting not only IL-23 (with risankizumab, tildrakizumab, or guselkumab) but also IL-12/23 (with ustekinumab) and IL-17 (with ixekizumab, secukinumab, or brodalumab).

In the final presentation, Prof Lluís Puig described clinical experience of targeting IL-23 in psoriasis and provided an overview of findings from several clinical trials, including: VOYAGE 1 and 2 (guselkumab versus the TNF inhibitor [TNFi] adalimumab); NAVIGATE (guselkumab versus ustekinumab); and the head-to-head ECLIPSE study (guselkumab versus secukinumab).

The symposium concluded with a lively panel discussion in which the speakers addressed a variety of questions and comments from the audience.

Introduction

The aim of this symposium was to familiarise participants with the IL-23 pathway and the rationale for targeting this pathway in PsA. Recent clinical and mechanistic data on targeting the IL-23 pathway in PsA were presented, and the real-world impact of these data on clinical practice was discussed, along with the effect of targeting the IL-12/23 pathway. Further aims were to increase participants' understanding of how data on targeting the IL-23 pathway in psoriasis relate to the treatment of PsA, and to highlight unmet needs in the management of PsA in the clinic.

The Promise and Delivery of Targeting the IL-12/23 Pathway

Doctor Stefan Siebert

Psoriatic disease is extremely heterogeneous, with inflammation affecting the skin, joints, axial skeleton, and entheses.[1] Genome-wide association studies have shown that psoriasis, and PsA in particular, are not only clinically but also genetically heterogeneous, yet the IL-12/23 and IL-17 pathways are implicated in the pathogenesis of both diseases.[2-4] For example, increased IL-23 expression triggers a T cell response (stimulating IL-22 and IL-17 expression) in the entheses that leads to osteoproliferation, inflammation, and both bone loss and ankylosis in mouse models.[3,4]

Efficacy of IL-12/23 inhibition by ustekinumab, which blocks the p40 subunit common to these two cytokines, has been demonstrated in both PsA (in the pivotal Phase III PSUMMIT studies) and psoriasis.[5-9] Integrated safety data from 12 randomised, controlled trials in psoriasis, PsA, and Crohn's disease in which 5,884 patients received ustekinumab showed that major adverse cardiovascular events, malignancies, and death were rare.[10] Moreover, preliminary analysis of real-world data in psoriasis, from PSOLAR (a global psoriasis register of 12,095 patients), shows that the drug with the longest survival (a surrogate marker of efficacy, safety, and tolerability) is ustekinumab, ahead of adalimumab, infliximab, and etanercept (Figure 1).[11] According to the PSOLAR data, cumulative incidence rates of the adverse events of special interest (malignancy, major adverse cardiovascular events, serious infections, and mortality) are relatively low with ustekinumab; the rate of serious infections is particularly low.[12]

In PSUMMIT 1 and 2, ustekinumab was associated with significant improvements in enthesitis and physical function measures.[5,13,14] Treatment with ustekinumab (45 mg or 90 mg) significantly reduced the Maastricht Ankylosing

Spondylitis Enthesitis Score (MASES) at 24 weeks (p=0.0019–<0.0001 versus placebo),[5] and this improvement in enthesitis was associated with improvement in physical function as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) and 36-item Short-Form Health Survey (SF-36).[14] Furthermore, in the head-to-head ECLIPSA study, significantly more patients treated with ustekinumab (73.9%) achieved a score of 0 on the Spondyloarthritis Research Consortium of Canada (SPARCC) scale at 6 months than TNFi-treated patients (41.7%; p=0.018; primary endpoint);[15] in the same study, reductions in tender joint count and swollen joint count were similar between the two treatment groups.[15]

Real-world treatment with ustekinumab in PsA has previously only been investigated in several small observational studies.[16-18] The PsABio study is a prospective observational cohort of patients with PsA from eight European countries who were starting ustekinumab or a TNFi as a first, second, or third-line biologic therapy (N=992);[19-21] 6-month, PsABio data presented at this EULAR Congress show that only 7.6% of patients on ustekinumab and 10.2% on a TNFi stopped or switched biologics within 6 months.[19] Ustekinumab and TNFi performed similarly well in achieving remission or low disease activity as assessed by measures including clinical Disease Activity in Psoriatic Arthritis (cDAPSA) remission, and minimal disease activity.[20] The mean swollen joint count in 66 joints was reduced from baseline by 4.3 (ustekinumab) and 4.5 (TNFi); and the tender joint count in 68 joints was reduced from baseline by 6.4 (ustekinumab) or 6.7 (TNFi).[22]

Dr Siebert concluded that IL-12/23 pathway inhibition with ustekinumab is well tolerated and effective across a range of domains, with low or minimal disease activity achieved and sustained in a significant proportion of patients with psoriatic disease. Nonetheless, PsA remains a difficult disease to treat; there are still unmet needs (e.g., lack of head-to-head trials, uncertainty about best treatment strategy for an individual). Experience of targeted therapies and real-world data from large cohorts will help advance understanding of the disease and lead to better patient outcomes.

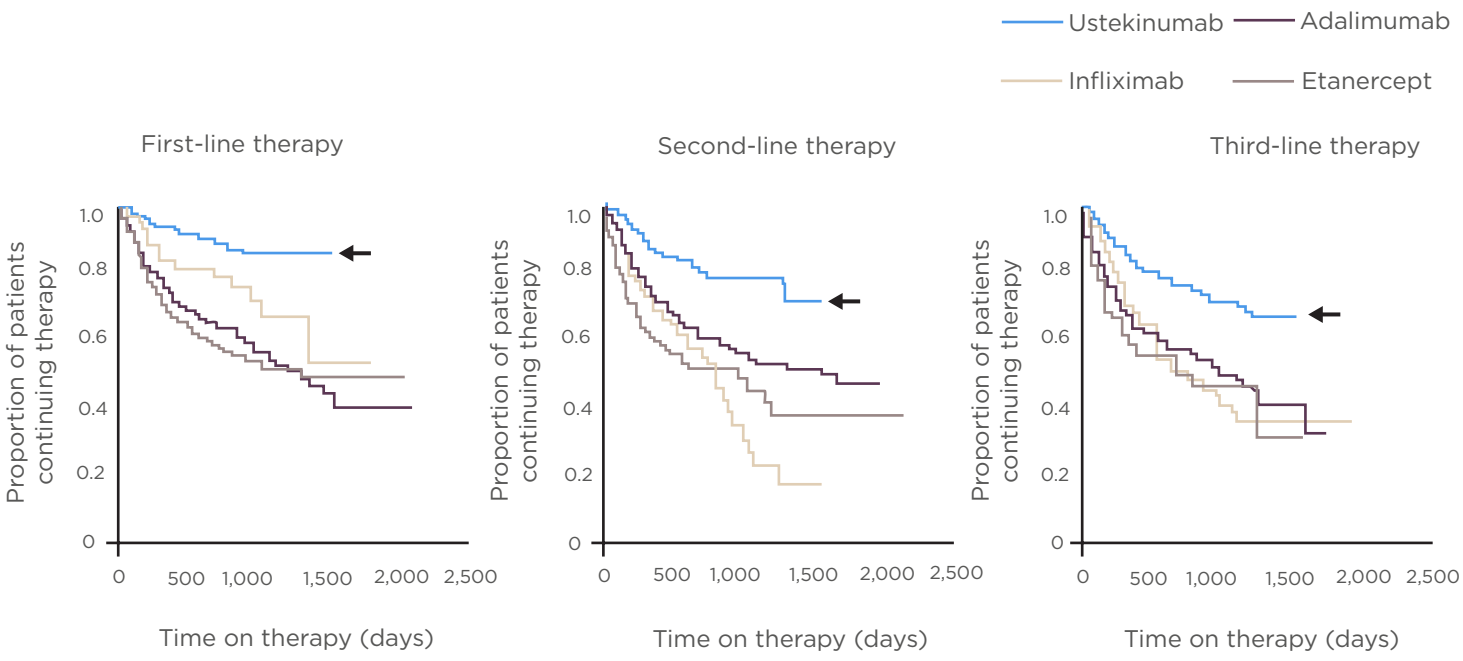


Figure 1: Drug survival in patients with psoriasis in PSOLAR.[11]

PSOriasis Longitudinal Assessment and Registry (PSOLAR) study: global psoriasis register of 12,095 patients, with ~4,000 patients initiating a new biologic therapy.

Focus on the IL-23 Pathway

Professor Georg Schett

IL-23, a dimer of p19 and p40 subunits, was identified in a relatively recent search for IL-6 family cytokines in sequence databases in 2000.[23] IL-23 is produced by antigen-presenting cells, mainly dendritic cells (DC); the skin contains numerous DCs and is, therefore, a major location of IL-23 production. DC also produce IL-12 (a dimer of p35 and p40); these cytokines together trigger the activation of T cells.[23,24] The key function of IL-23 is to induce T cell proliferation.[23]

Whether DC predominantly produce p19 or p35 (and, therefore, IL-23 or IL-12, respectively) depends upon their cellular and molecular environment; p19 production can be linked to autoinflammatory disease.[25] For example, in a murine model of multiple sclerosis, increased p19 expression induces experimental autoimmune encephalomyelitis and triggers T helper Type 17 (Th17) cell differentiation, thus exacerbating autoimmune-triggered inflammation.[25]

IL-23 triggers psoriasis and entheseal inflammation in humans;[4,26] analysis of skin from patients with psoriasis shows that p19 and p40 are upregulated in lesional skin.[27] This finding suggests that IL-23 is produced *in situ* in inflamed skin.[27] Importantly, if p19 is blocked in skin, hyper-proliferation, skin thickness, and skin infiltration by CD4+ and CD8+ T cells are significantly reduced (all $p<0.01$–<0.05 versus placebo), but resident Langerhans cells are unaffected.[28] Targeting p19, therefore, has an anti-inflammatory effect achieved by downregulation of a network of key pathogenic immune pathways in psoriasis and PsA such as T cell chemotaxis (e.g., the chemokine CCL20), neutrophil chemotaxis (e.g., the chemokine CXCL8), IL-17 pathway activation (e.g., the IL-17 target gene *lipocalin 2*) and innate immune activation (e.g., the alarmin S100A7, also known as psoriasin).[28] Interestingly, preclinical studies have shown that the p19 subunit also dimerises with an Epstein–Barr virus-induced protein to form IL-39,[29,30] but there is no evidence yet that IL-39 has a biological function in humans.[30,31]

As mentioned, IL-23 also has a key role in enthesitis.[32] When triggered by mechanical stress, disturbed barrier function, or infections, IL-23 (with prostaglandin E2) stimulates the accumulation of IL-17-producing γδ T cells.[33] Production of IL-17, TNFα, and IL-22 by γδ T cells, along with Type 3 innate lymphoid cells, instigates enthesitis.[34] Enthesitis-driven PsA is highly sensitive to IL-12/23 inhibition by ustekinumab, as shown by reductions from baseline in SPARCC score, MASES, and Leeds Enthesitis Index (LEI) score in the ECLIPSA study.[15]

In autoimmunity, IL-23 controls the pathogenicity of antibodies by regulating their glycosylation (sialylation) and, thus, their effector function, essentially 'unlocking' them for use.[35] Under conditions of high sialylation of IgG, autoantibodies are in a non-inflammatory or 'locked' state, and asymptomatic autoimmunity results in mice.[34] Under conditions of low sialylation of IgG, inflammatory autoantibodies are 'unlocked' and autoimmune disease results.[35] In a IL-23 knockout mouse model of collagen-induced arthritis, the production of key effector cytokines of inflammation (TNFα, IL-6, and CXCL1) was impaired when the IgG was in its sialylated ('locked') state, suggesting that autoimmune inflammation is at least partly controlled by IL-23.[35] Interestingly, IL-23 deficiency mitigates experimental lupus in mice.[36]

Prof Schett concluded that IL-23, produced by DC and other innate immune cells, polarises T cells to a Th17 phenotype, thereby influencing downstream adaptive immune responses. The role of IL-23 in skin and entheseal inflammation, T/B-cell interaction, and auto-antibody effector function suggests therapeutic value of IL-23-targeting in autoimmune and autoinflammatory disease.

Targeting IL-23: What Could This Mean in Practice?

Professor Peter Taylor

The efficacy of biologic and small-molecule treatments in PsA has been evaluated in multiple clinical trials in patients with predominantly skin and/or joint involvement. All licensed drugs have significantly better efficacy in terms of joint outcomes, as assessed by rates of 20% improvement in American College

of Rheumatology criteria (ACR20) at Week 24, versus placebo (drug classes: TNFi, IL-17 inhibitors, and ustekinumab; ACR20 rates range: 36.6–63.8%; p value range: ≤0.001–<0.0001).[5,37-44]

The IL-17 family (IL-17A, IL-17A/F, and IL-17F), along with IL-25, signal via the IL-17 receptor.[45,46] Approved drugs, ixekizumab and secukinumab, block IL-17A; brodalumab blocks the IL-17 receptor so potentially affects IL-17A, IL-17F, and IL-25; bimekizumab (in development) blocks IL-17A/F.[46] Clinical trial data on these drugs are crucial to understanding how clinical findings relate to the underlying pathophysiology of psoriatic disease.

Phase III trials of secukinumab (FUTURE 2) and ixekizumab (SPIRIT P1) show that in patients with PsA, IL-17A inhibition significantly improved joint and skin outcomes, as assessed by ACR and Psoriasis Area and Severity Index (PASI) 75 response rates at Week 24 (all p<0.001 versus placebo).[39,44] Additionally, in a Phase II trial of brodalumab in patients with PsA, improvement in joint outcomes at Week 12 (p<0.05 versus placebo) was sustained to Week 108.[47,48] Conversely, IL-17A/F blockade has been reported to lead to impaired immunity to fungal and extracellular bacterial infections,[49] and in some studies in Crohn's disease, gut symptoms were exacerbated by treatment with IL-17 inhibitors.[50-52]

Targeting upstream of IL-17 with ustekinumab enables reduction in T-helper cell activity (Th1 and Th17) and subsequent IL-17 expression.[53,54] In patients with PsA naïve to biologics (PSUMMIT 1), ustekinumab significantly improved ACR response rates versus placebo at Week 24 (p≤0.0001 for ACR20, 50, and 70).[5] Moreover, in patients already exposed to a biologic (i.e., TNFi, PSUMMIT 2), ACR response rates were slightly lower than observed in PSUMMIT 1 but significantly better with ustekinumab than placebo (ACR20, p<0.001; ACR50, p<0.05).[5,7]

IL-23 is targeted by risankizumab, tildrakizumab, and guselkumab.[54] Blocking IL-23 alone is expected to block intracellular signals from Th17 but not Th1 cells.[53,54] In patients with rheumatoid arthritis (RA), blocking IL-12/23 (ustekinumab) or IL-23 (guselkumab) in a Phase II study did not achieve the primary endpoint (ACR20 at Week 28),[55] suggesting that RA and PsA are distinct diseases that involve different pathways in their aetiology; however, results from Phase II trials examining IL-23 inhibition in PsA have demonstrated, and importantly retained, efficacy.[56,57] For example, patients with PsA receiving one single dose of the anti-IL-23A antibody risankizumab at baseline had significantly better ACR20 response rates at Week 16 versus placebo (p<0.05).[56]

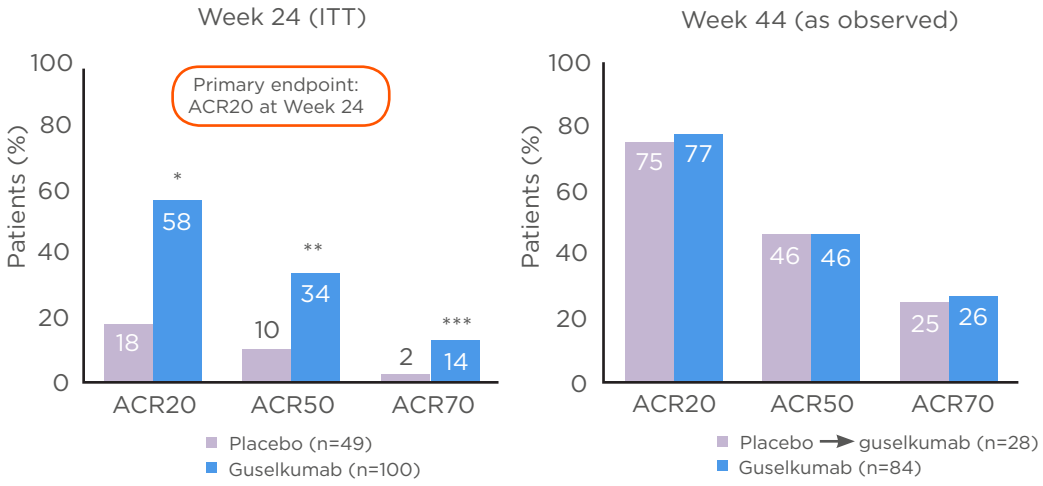


Figure 2: Guselkumab treatment led to significant improvements in ACR outcomes versus placebo at Week 24 in patients with psoriatic arthritis. Patients switching from placebo to guselkumab at Week 24 had similar outcomes to the guselkumab group at Week 44.[57]

*p<0.0001; **p=0.0021; ***p=0.023 versus placebo.

ACR: American College of Rheumatology criteria; ITT: intention to treat population.

Retained efficacy, even after switching from placebo, is evident with guselkumab in PsA.[57] In a Phase II study, patients with PsA were randomised to guselkumab or placebo then crossed over to guselkumab at Week 24.[57] Treatment with guselkumab resulted in significant improvement in joint and skin outcomes at Week 24 as assessed by ACR (Figure 2) and PASI.[57] At Week 44, ACR responses in patients who switched to guselkumab caught up with results in the group who initiated guselkumab at baseline (Figure 2).[57] Rates of patients reaching these endpoints increased with time, and at all response levels the benefit was sustained for several months after treatment.[57]

Treatment with guselkumab also resulted in significant improvements in physical function at Week 24 (HAQ-DI score; p=0.0002 versus placebo) and resolution of enthesitis (p=0.0120) and dactylitis (p<0.0010).[57] Notably, patients had significant improvement in mental as well as physical aspects of quality of life (as measured by the SF-36), perhaps reflecting the dramatic improvement in their skin symptoms.[57] Guselkumab was generally well-tolerated through to Week 56, and serious adverse events were rare.[56] No injection site reactions were reported.[57]

Prof Taylor concluded that the IL-23 and IL-17 pathways are promising therapeutic targets in PsA. The availability of targeted therapies and advances in engineering techniques has facilitated dissection of pathobiological disease components to provide insights into the 'immunotaxonomy' of rheumatic diseases, and some understanding of the clinical correlates of that information. Further advances in precision medicine and biomarkers to inform treatment decisions will change disease management, but until then, optimal therapy for patients will depend on certain comorbidities (e.g., inflammatory bowel disease [IBD], uveitis) and whether they predominantly have skin or joint symptoms. The benefit:risk ratio of emerging therapies is not yet clear, and we await emerging Phase III data.

Experience of Targeting IL-23 in Dermatology

Professor Lluís Puig

In psoriasis, an autoimmune process that depends on IL-23 leads to differentiation of naïve T cells to Th17 cells, promoting the production of IL-17.[58] Subsequent activation of keratinocytes produce a variety of chemotactic factors in a feed-forward mechanism that sustains the inflammatory process in psoriatic skin.[58] This process can be controlled, but tissue resident 'memory cells' that express IL-23 receptor can be rapidly reactivated to reproduce psoriatic lesions.[58] Thus, IL-23 is the 'master switch' for the inflammatory process underlying psoriasis.

Prof Puig suggested that upstream targeting (i.e., IL-23) may be more convenient, allowing less frequent dosing and less need for induction treatment. Therapeutic longevity (i.e., maintenance of response over time) is typical of IL-23 inhibition but less so with IL-17 blockade. Furthermore, the causal relationship between IL-17 inhibition and exacerbations of IBD and/or candidiasis is inconclusive.

In VOYAGE 1 and 2, guselkumab treatment was efficacious and high levels of response (PASI 90 and PASI 100) were maintained for up to 156 weeks in patients with psoriasis, even after switching from placebo (at Week 16) or TNFi (at Week 28) to guselkumab.[59–61] VOYAGE 1 was a three-arm trial in which patients were randomised to guselkumab, adalimumab, or placebo then crossed over to guselkumab at Week 16.[59] VOYAGE 2 was similar in design to VOYAGE 1; however, at Week 24, patients were re-randomised, depending on their response: responders (PASI 90) were randomised to (continue) guselkumab or placebo then crossed over to guselkumab upon loss of ≥50% of their Week-28 PASI response.[60]

In both studies, approximately 70% of patients with psoriasis achieved PASI 90 with guselkumab at Week 16, and by Week 24 rates were significantly higher for guselkumab than adalimumab (p<0.010).[59,60] PASI 100 rates increased with time,[59,60] reaching approximately 50% for guselkumab-treated patients at Week 48.[59] Importantly, patients switching to guselkumab from placebo at Week 16 showed

significantly higher PASI 90 and 100 rates than for adalimumab by Week 48 (p<0.001).[59] Additionally, guselkumab maintained response rates to Week 156, with approximately 80% and 50% of patients achieving PASI 90 and 100, respectively.[61]

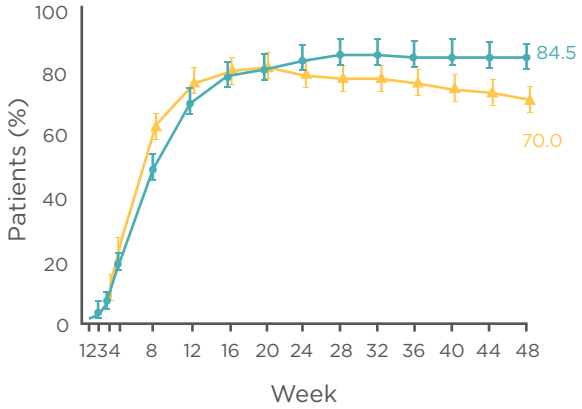
Patients who did not achieve PASI 90 on adalimumab achieved and maintained PASI 90 after the switch to guselkumab.[62] Of the patients who did not reach PASI 90 at Week 52 and 28 in VOYAGE 1 and 2, respectively, after switching to guselkumab, >70% had reached PASI 90 and >40% PASI 100 at Week 100. These findings show that guselkumab is effective not only as a first-line therapy but also as a second-line therapy after adalimumab.[62,63]

Guselkumab is also effective after a suboptimal response to ustekinumab, as demonstrated in NAVIGATE.[64] Patients received open-label ustekinumab and, depending on Investigator's Global Assessment score (IGA), were randomised to guselkumab or ustekinumab (IGA≥2); those with IGA 0 or 1 continued ustekinumab.[64] Between Weeks 20 and 52, improvements in IGA ≥0/1, PASI 75, 90, and 100 response rates were higher in patients who switched to guselkumab than in those who continued ustekinumab.[64]

Therapeutic longevity is shown with guselkumab in patients who, after achieving PASI 90, were randomised to placebo in the VOYAGE 2 study.[60,65] At 6 months after their last injection of guselkumab, approximately 50% of patients maintained PASI 90 and 30% maintained PASI 100 after 5.5 months.[60] Of the patients who lost >50.0% of their initial response after withdrawal of guselkumab, 87.6% regained PASI 90 by Week 28 after restarting guselkumab.[65]

In the head-to-head ECLIPSE study, patients with psoriasis (excluding those with a history of IBD) were randomised to guselkumab or secukinumab.[66] By Week 48 there was an approximately 14.0% higher rate of PASI 90 response to guselkumab than to secukinumab (p<0.001; Figure 3).[66] The safety of the two drugs through Week 56 was comparable but generally better with guselkumab than with secukinumab.[66] There was a slightly higher rate of infections with secukinumab (64.8%, versus guselkumab: 58.6%), and IBD developed in 3 of the 511 patients in the secukinumab group (versus none in the guselkumab group).[66]

In conclusion, Prof Puig suggested that guselkumab is suitable for first-line treatment in patients with psoriasis, for second-line treatment after failure of adalimumab, and for patients with an insufficient response to ustekinumab. Responses to guselkumab are persistent over time and highly sustainable, and guselkumab has been superior to secukinumab (demonstrated by PASI 90 response rate at Week 48) in long-term studies. Guselkumab is efficacious, convenient (injected at Weeks 0 and 4, then every 8 weeks), and well tolerated (comparable with ustekinumab).



	Guselkumab	Secukimunab
Randomised patients, n	534	514
PASI 90 responders, n (%)	451 (84.5)	360 (70.0)
Treatment difference, % (95% CI)	—	14.2 (9.6–18.8)
p value	—	<0.001

Guselkumab 100 mg (n=534)
Secukinumab 300 mg (n=514)

Figure 3: Guselkumab treatment led to significantly higher response rates of PASI 90 (with 95% CI) versus secukinumab through Week 48 in patients with psoriasis.[66]

Non-responder imputation was used for missing data.

CI: confidence interval; PASI: Psoriasis Area and Severity Index.

Panel Discussion and Concluding Remarks

The faculty responded to a variety of questions during the panel discussion. The audience members were interested in the treatment decision-making process and asked the panel about the ideal patient for ustekinumab treatment. Prof Puig suggested that patients with extensive skin disease, as well as enthesitis, dactylitis, and peripheral arthritis, would be suitable for ustekinumab, but it has failed to show efficacy in patients with axial spondyloarthritis. Dr Siebert added that it is important to consider safety in patients with multiple comorbidities; ustekinumab's safety profile makes it a suitable treatment for patients with skin disease and enthesitis who also experience complications due to comorbidities.

Prof Puig pointed out that clinical trial findings regarding entheseal disease are dependent on patient-reported outcomes, and although there are promising data on IL-23 blockade in enthesitis, the apparent lack of effect in axial disease is puzzling. Prof Schett explained that this may be due to different environments in different tissues (e.g., skin, spine, and peripheral entheseal tissue), with differences in IL-23 producing cells. It needs to be considered that spinal disease is probably not just one disease, but differences between axial spondyloarthritis and PsA need to be considered. In support of this concept, he emphasised that a post-hoc analysis of PSUMMIT data showed that patients with PsA and concomitant axial disease responded to treatment,[67] further evidence that there may be differences in axial disease patterns between classic ankylosing spondylitis and axial involvement in PsA. Dr Siebert agreed that there may be some IL-23-independent production of IL-17, and head-to-head studies are needed to better understand PsA.

The audience asked about the low malignancy rates seen with targeted therapies, and whether these differ from those in the US Food and Drug Administration (FDA) database. Dr Siebert called for caution when comparing real-world and clinical trial data, due to differences in patient populations. Prof Puig noted that no increase in risk of malignancies has been noted with targeted therapies in patients with psoriasis, except for one epidemiologic study, showing an increased risk of non-melanoma skin cancer in patients treated with anti-TNF agents;[68] these patients are likely to have been exposed to coal tar, photochemotherapy, and cyclosporin, which increase their risk.

When asked about switching therapies after inadequate response, and the optimal treatment sequences in difficult-to-treat patients, the faculty responded that the current best approach is to switch to a treatment with a different target. Patients who seem to develop antidrug antibodies might be switched to one of the less immunogenic treatments. The faculty noted that switching decisions are based on whether the relapse is predominantly skin, peripheral joint or axial disease, with a need for more finely tuned therapy in PsA than in RA.

Prof Taylor commented that in some countries biosimilar use is encouraged to achieve cost savings, though patients with comorbidities may benefit more from other options. Dr Siebert added that patients with PsA are generally more risk-averse and less tolerant of side effects than patients with arthritis. Prof Schett agreed that, with the availability of distinct immune interventions and the possibility to tailor patient-specific treatments, it would be a pity if choices would be merely dictated by costs.

According to Prof Puig, it should be possible to prescribe treatments other than anti-TNF as first-line therapy, especially for those patients in whom infection might decompensate their pre-existing comorbidities. He emphasised the importance of finding the immunological mechanism underlying the skin disease, enthesitis, or joint disease, and eventually making treatment decisions based on this information. Prof Taylor, who closed the discussion, noted that rheumatologists and dermatologists will still face several challenges in their treatment decision processes in the future.

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Abstract Reviews

Our congress team have handpicked some of their favourite abstracts from this year's EULAR congress; read the presenters' summaries below.

Efficacy and Safety of E6011, an Anti-Fractalkine Monoclonal Antibody, in MTX-IR Patients with Rheumatoid Arthritis

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Fractalkine (CX_3CL1, designated as FKN hereafter) is the sole member of the CX_3C chemokine family which leads to dual actions, chemotaxis, and cell adhesion for leukocytes expressing the cognate receptor CX_3CR1. The authors have conducted clinical trials of E6011, a novel humanised anti-FKN monoclonal antibody, for patients with rheumatoid arthritis (RA) in Japan.[1] This is the first report of results of efficacy and safety for E6011 from a Phase II, multicentre, randomised, double-blind, placebo-controlled, parallel-group comparison study in RA patients inadequately responding to methotrexate (MTX-IR).[2]

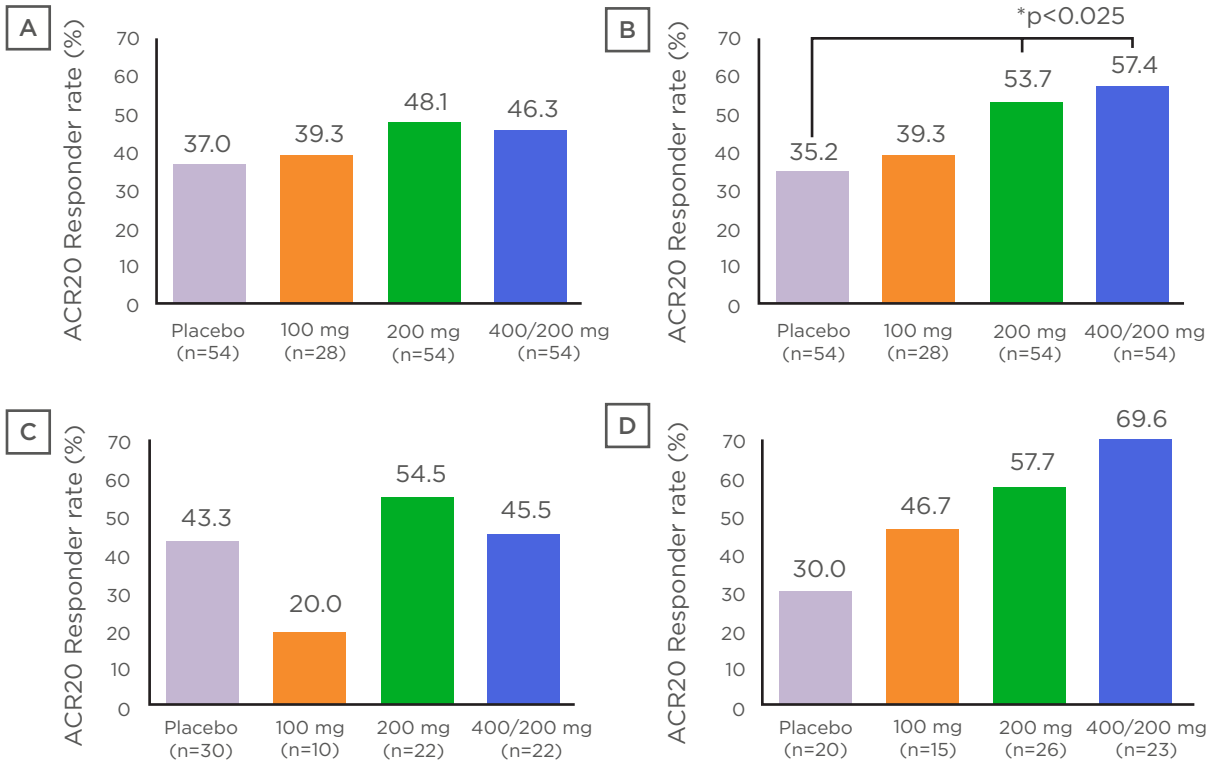

Figure 1: ACR Response rate at Week 12 (A), Week 24 (B) (NRI), Week 24 in MTX-IR RA patients with lower (C) and higher (D) baseline CD16+ monocytes (NRI)

ACR20 response rate at Week 12 was higher in the 200 mg group and 400/200 mg group than the placebo group. However, a statistically significant difference from placebo was not found. ACR20 response rate at Week 24 was statistically significantly higher in the 200 mg group and 400/200 mg group than the placebo group (p=0.023 for the 200 mg group, p=0.01 for the 400/200 mg group; a logistic regression model with Hochberg method). ACR20 response rate at Week 24 in subjects with low baseline CD16+ monocytes (<10.35%) were 43.3% (13/30 subjects) in the placebo group, 20.0% (2/10 subjects) in the 100 mg group, 54.5% (12/22 subjects) in the 200 mg group, and 45.5% (10/22 subjects) in the 400/200 mg group, respectively. ACR20 response rate at Week 24 in subjects with high baseline CD16+ monocytes (≥10.35%) were 30.0% (6/20 subjects) in the placebo group, 46.7% (7/15 subjects) in the 100 mg group, 57.7% (15/26 subjects) in the 200 mg group, and 69.6% (16/23 subjects) in the 400/200 mg group, respectively.

During the 24-week double-blind period, 190 patients in total with moderate-to-severe active RA of MTX-IR were randomly assigned to E6011 (100 mg: n=28, 200 mg: n=54, and 400/200 mg: n=54) or placebo (n=54) at a 1:2:2:2 ratio. In the E6011 100 mg, 200 mg, and placebo groups, subjects received E6011 at Weeks 0, 1, 2, respectively, and every 2 weeks subsequently. In the E6011 400/200 mg group, subjects received 400 mg at Weeks 0, 1, 2, 4, 6, 8, 10, and then 200 mg every 2 weeks subsequently.

The ACR20 response rate at Week 12 (non-responder imputation), the primary endpoint, was not statistically significant (Placebo: 37.0%, 100 mg: 39.3%, 200 mg: 48.1%, and 400/200 mg: 46.3%). However, statistically significant difference from placebo in ACR20 response rate was found in the 200 mg and 400/200 mg groups at Week 24 (Placebo: 35.2%, 100 mg: 39.3%, 200 mg: 53.7%, and 400/200 mg: 57.4%). In addition, the authors focussed on CD16+ monocytes which highly expressed FKN receptor/CX3CR1 as a blood biomarker and are linked to the clinical response to E6011. Exploratory, the whole patient population was divided into 2 groups according to the median value of baseline CD16+ monocyte percentage (median: 10.35%). Much clearer ACR20 responses were observed in a dose dependent manner in the subjects who showed higher baseline CD16+ monocytes over the median at Week 24 (NRI) (Placebo: 30.0%, 100 mg: 46.7%, 200 mg: 57.7%, and 400/200 mg: 69.6%), although such fashion was obscure in the subjects below the median value. Adverse events that occurred in ≥5% of subjects in any E6011 group were nasopharyngitis, upper respiratory tract infection, stomatitis, bronchitis, back pain, pharyngitis, and dental caries. E6011 was well tolerated with no notable safety concerns at doses of 100, 200, and 400/200 mg when administered subcutaneously for 24 weeks.

In conclusion, E6011 provided clinical improvements with a good safety profile in RA patients with MTX-IR (Figure 1). Notably, a higher efficacy of E6011 was suggested in patients with higher baseline CD16+ monocytes (%). This is novel evidence suggesting that this new approach to targeting FKN/CX_3CR1 interaction could be beneficial for RA.

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Comparative Effectiveness Research in Observational Settings: Evaluating Two New Methods to Analyse Response Rates

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ABSTRACT

Observational studies are being used more frequently to compare drug effectiveness. Authors typically report the proportion of patients reaching a defined clinical threshold or response rates (e.g., American College of Rheumatology [ACR] response or clinical disease activity index [CDAI] low disease activity rates) after a set time. Comparing response rates in that setting is hampered by two major threats. Firstly, patient, disease, and treatment characteristics often differ for each treatment group. Secondly, assessing drug maintenance after a certain period of time excludes the analysis from all of the patients who discontinued their treatment for ineffectiveness or intolerance, thus resulting in an attrition bias, which may overestimate drug effectiveness. While several methods have been proposed, none account for both confounding and attrition.

The aim of this study was to propose two new methods, propensity-score matched LUNDEX (PSM-LUNDEX) and CARRAC, to adequately compare response rates in patients with different baseline characteristics, while accounting for attrition, and compare them to established methods (complete case [CC] analysis and LUNDEX).

The different methods are illustrated using CDAI low disease activity (≤10) rates in data from a collaboration of registries, using 3,448 patients treated by a biologic, either intravenously (n=2,414) or subcutaneously (n=1,034).[1]

The first method is CC, where the response rate is computed as the percentage of responders in

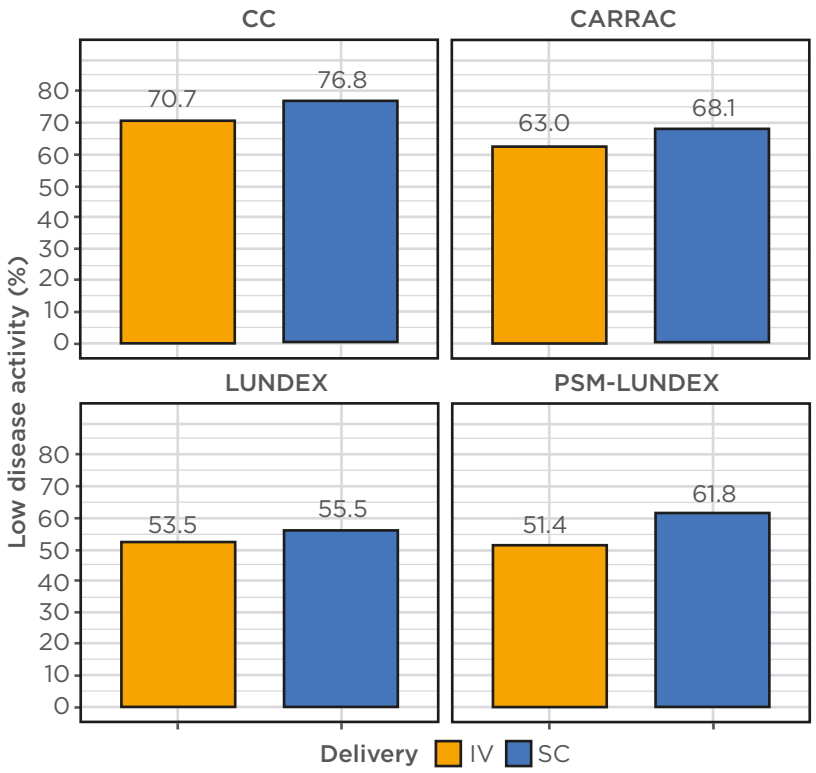

Figure 1: Estimated response rate between intravenous and subcutaneous biologic by estimation method.

CARRAC: confounder-adjusted response rate with attrition correction; CC: complete case analysis; IV: intravenous; PSM: propensity score matching; SC: subcutaneous.

total number of patients still on the treatment at the given time point.

The second method is the LUNDEX,[2] in which CC is corrected for attrition by multiplying it by the Kaplan-Meier estimates of the survival, thus considering all patients not on treatment as non-responders.

The third method is PSM-LUNDEX, in which the patients are firstly selected in both exposure groups using PSM, and then the LUNDEX is used to compute the response rate.

The fourth method is called confounder-adjusted response rate with attrition correction (CARRAC) by reason for drug discontinuation. This method firstly computes estimates of drug survival for the main reasons of drug discontinuation, such as ineffectiveness, adverse events, and remission. Then, it estimates the response rate using random effect individual patient data meta-analysis with estimates for each reason of drug discontinuation, combined using weights of the first step.

Estimated response rates differed by >20%, depending on the method used (Figure 1). Compared to CC, both PSM-LUNDEX and LUNDEX methods yielded much lower response rates, while the CARRAC method estimated response rate was between these estimates. Compared to CC analysis, differences in response between the intravenous and subcutaneous groups were smaller for the LUNDEX methods, larger for PSM-LUNDEX, and close to CC for the CARRAC method.

Both LUNDEX methods underestimate the true response rates by considering all patients stopping treatment as non-responders, while CC overestimates it by considering patients stopping as having a similar response rate to patients continuing treatment. The CARRAC method, which accounts for attrition by reason for drug discontinuation, obtained response rate estimates in between CC and LUNDEX corrections.

There are limitations for each method. CC does not correct for confounding or attrition bias; LUNDEX does not correct for confounding; for PSM-LUNDEX, overlapping propensity score only allowed selection of 561 patients per group; and CARRAC requires information on reason for stopping. Several other analyses, such as inverse probability weighting or instrumental variable, should be examined to obtain confounder and attrition-adjusted estimates of response rate. Furthermore, simulation studies are needed to assess the most accurate estimation method.

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Circulating T Cell Clones in Preclinical Phases of Rheumatoid Arthritis

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Keywords: Preclinical phases, rheumatoid arthritis (RA), T cell receptor.

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BACKGROUND AND AIMS

The aetiopathogenesis of rheumatoid arthritis (RA) is only partially understood, but is believed to result from a multi-step process, whereby in genetically susceptible individuals, environmental factors induce a pathological activation of the immune system that may eventually lead to systemic autoimmunity and subsequent clinical onset of the disease.[1] Current evidence suggests that the immune onset of RA takes place outside of the joints several years before clinical manifestations and that primed memory T cells migrate from the peripheral blood into the synovial joints, where they are probably activated by cross-reactivity with auto-antigens expressed in joints and clonally expand. Indeed, expanded T cell clones can be found in the synovial tissue of established RA patients.[2,3] The aim of this study was to examine if expanded T cell clone signatures can be detected in the peripheral blood before the development of clinical RA.

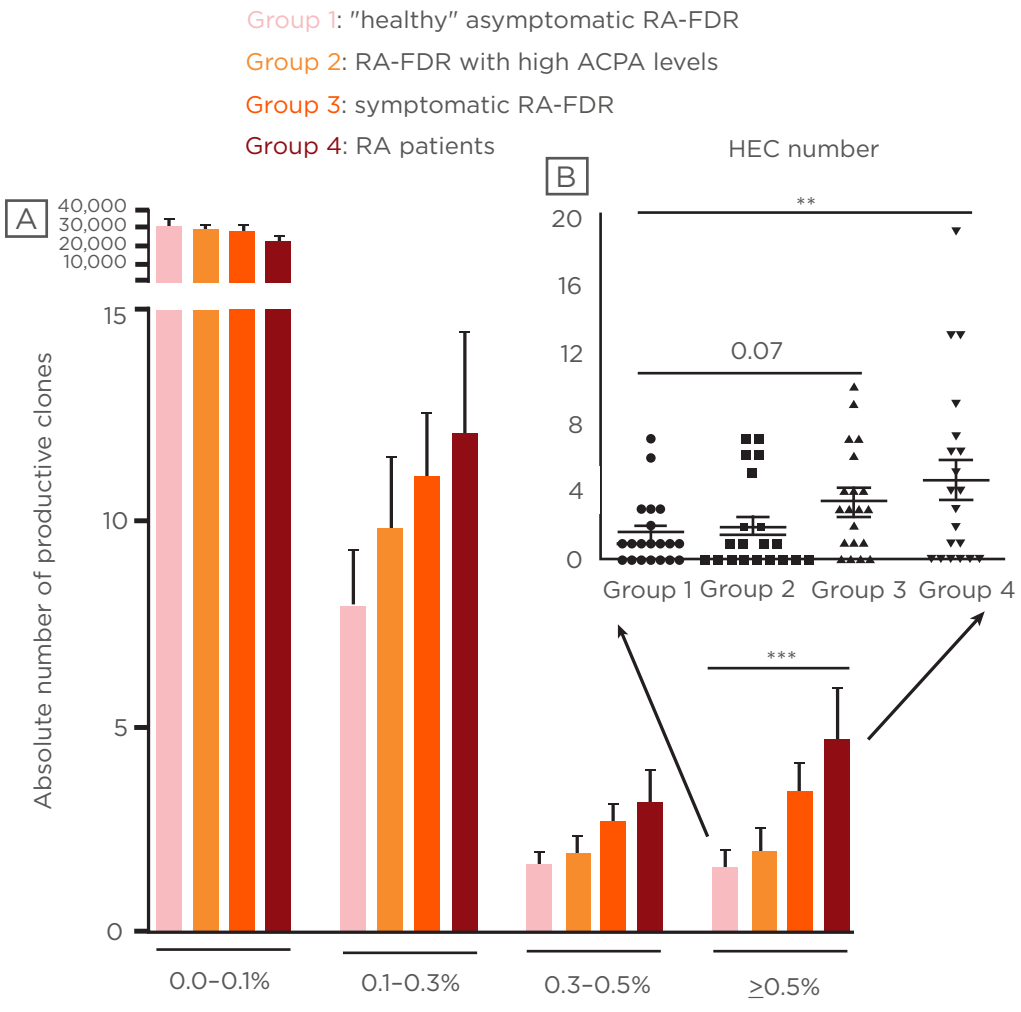

Figure 1: Absolute number of productive T cell receptor clones by clonal size.

(A) Bars show mean and SEM for clones at different frequency cut-offs. (B) Each dot represents the number of HEC observed for one individual (group mean and SEM are shown as line and error bars).

ACPA: anti-citrullinated peptide antibodies; HEC: highly expanded clones; SEM: standard error of the mean; RA: rheumatoid arthritis; RA-FDR: first-degree relatives of RA patients.

**p<0.01, ***p<0.001 using a mixed effect regression model to account for matching.

METHODS

Next-generation sequencing of the T Cell Receptor β (TCRβ) complementarity-determining region 3 (CDR3) repertoire was performed on genomic DNA isolated from blood samples of individuals genetically at risk for RA, namely first-degree relatives of RA patients (RA-FDR) at different preclinical phases of disease development (SCREEN-RA cohort),[4] and of matched RA patients used as a control group (SCQM cohort).[5,6] The European League Against Rheumatism (EULAR) recommendations for terminology were used to categorise RA-FDR in preclinical RA stages.[7] All individuals were matched for age and sex, and categorised into four groups (n=20/group): Group 1: 'healthy' asymptomatic RA-FDR without autoantibodies and symptoms associated with possible RA. Group 2: Asymptomatic RA-FDR with evidence of 'systemic autoimmunity associated with RA' defined by high levels of anti-citrullinated peptide antibodies (≥3 times the upper limit of normal of the ELISA test). Group 3: RA-FDR having presented undifferentiated arthritis (n=8) or having developed classifiable RA after inclusion (RA-converters, n=12). Group 4: patients with established RA of <3 years duration. T cell clones were characterised by their unique TCRβ CDR3 sequence and their degree of expansion (frequency). Clones with a frequency >0.5% were considered to be highly expanded clones (HEC). Both absolute number and frequency of productive T cell clones was compared between the four groups using mixed effect regression models to account for matching.

RESULTS

Expanded circulating TCR clones (>0.1%) tended to occur more frequently in patients in later preclinical stages of RA or with established RA (Figure 1A). Specifically, the absolute number of HEC was significantly higher in RA patients (mean 4.65%) and tended to be higher in symptomatic RA-FDR (mean 3.4%) compared to 'healthy' RA-FDR (mean 1.55%, p=0.003 and p=0.07, respectively) (Figure 1B). Asymptomatic at-risk individuals with strong RA-associated systemic autoimmunity did not differ from 'healthy' RA-FDR in terms of absolute number and frequency of clones. Finally, the number of HEC tended to be slightly higher around the time of RA onset, but specific clones were not shared within or between the different groups (data not shown).

CONCLUSIONS

Highly expanded T cell clones were detected in the peripheral blood of at-risk individuals before the clinical onset of RA, particularly in the later preclinical phases of RA development. Tracking these dominant T cell clones in longitudinal analyses and elucidating their role might help to better understand the earliest pathogenic events in RA.

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Comparison of PAXgene and Tempus Whole Blood RNA Collection and Isolation Systems for the Quantification of Type I Interferon-Stimulated Gene Expression

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ABSTRACT

Type I IFN have important roles in many paediatric and adult rheumatic diseases and are a new therapeutic target for which several anti-IFN treatments are currently in use or in development. Since the direct detection of these proteins in biological samples has proved challenging, indirect methods are often used to infer the presence of type I IFN. Most commonly this involves quantification of the relative expression of interferon-stimulated genes (ISG) that are used to calculate an interferon score (IS).[1] This score has been used for example to asses type I IFN activity in paediatric patients with type I interferonopathies, systemic lupus erythematosus, dermatomyositis, and systemic juvenile idiopathic arthritis.[2] Both quantitative PCR (qPCR) and NanoString technology have similar sensitivity and reproducibility for IS determination.[3] The use of different whole blood RNA collection systems on the IS has not been evaluated despite evidence of method-dependent changes in gene expression.[4]

The aim of the study presented at the European League Against Rheumatism (EULAR) 2019 congress in Madrid, Spain, was to compare expression of six common ISG (*IFI27, IFI44L, IFIT1, ISIG15, RSAD2, and SIGLEC1*) and the corresponding IS in RNA derived from two commonly used whole blood RNA collection systems (PAXgene [PreAnalytiX, Becton Dickinson] and Tempus [Applied Biosystems]).

For the purpose of the study, whole blood was collected from 10 healthy individuals (median age 25.5 years) in sodium heparin tubes and incubated with or without recombinant human IFN alpha 2b (rhIFNα, 2 IU/mL, 4 hours, 37 °C, 5% CO_2). Next, samples were divided between PAXgene and Tempus tubes and RNA was isolated according to the manufacturer's protocols. cDNA was synthesised (~500ng input RNA; qScript cDNA synthesis kit) and ISG expression measured on a QuantStudio 6 Real-Time PCR instrument using a TaqMan Fast Advanced Assay. For each ISG, expression was normalised against the geometric mean of two housekeeping genes (18s rRNA and HPRT1) and calculated using the formula 2-ΔCt. Relative gene expression was reported as the normalised expression of each ISG divided by the median of normalised expression of the same ISG in unstimulated samples. The median relative expression of all six ISG was used to calculate the IFN score for each sample.

The results showed that there was no statistically significant difference in the expression of any of the six ISG in either the rhIFNα-stimulated or unstimulated samples derived from PAXgene or Tempus tubes. Overall there was a strong correlation of the IFN score between PAXgene and Tempus tubes for both the unstimulated (R^2=0.9117, p<0.0001) and rhIFNα-stimulated samples (R^2= 0.8529, p=0.0001).

Despite reported differences in gene expression patterns associated with samples collected in PAXgene versus Tempus tubes, the results demonstrated that 6-gene IFN scores do not differ significantly between RNA samples obtained with these two systems. These results suggest that health care and research centres

can use either tubes for IFN score determination using these 6 ISG and results can be directly compared irrelevant of the RNA collection system employed.

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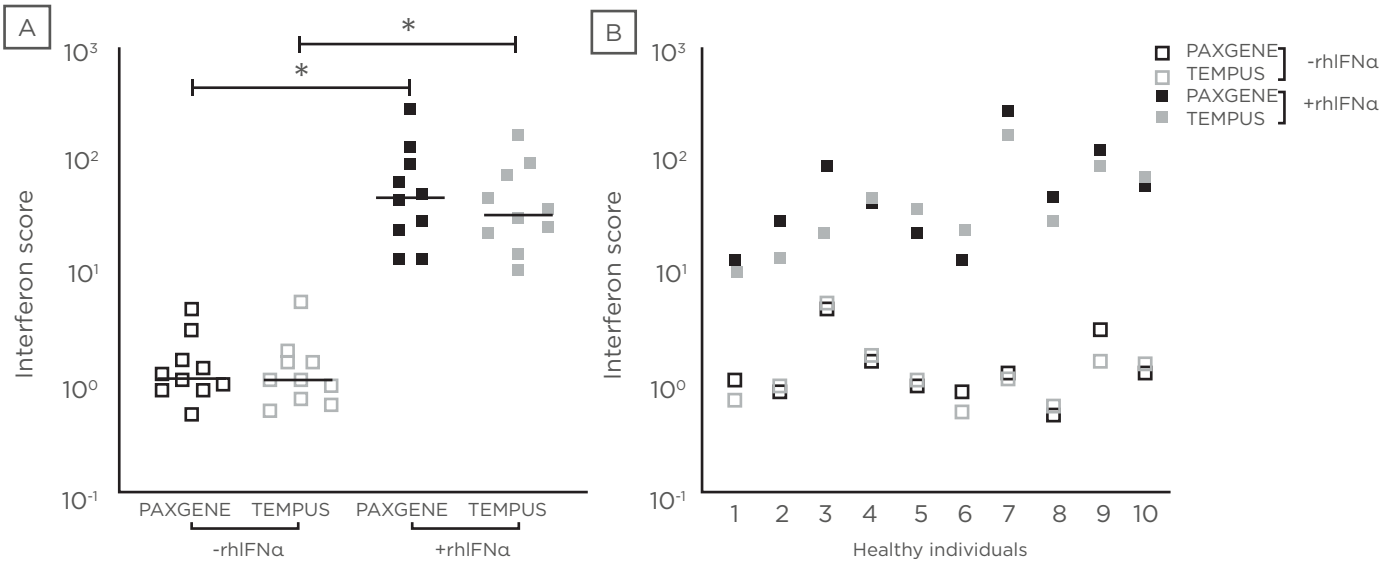

Figure 1: Interferon score derived from PAXgene and Tempus tubes.

Interferon score (y-axis) calculated for 10 healthy individuals (x-axis; A) following 4-hour *ex vivo* incubation of whole blood in the absence (open squares) and presence (solid squares) of rhIFNα and subsequent collection in PAXgene (black) and Tempus (grey) tubes (x-axis; B). Horizontal lines represent the median interferon score (n= 10; B). *indicates p <0.005.

Effects of Successive Switches to Different Biosimilars Infliximab on Immunogenicity in Chronic Inflammatory Diseases in Daily Clinical Practice

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Immunogenicity constitutes an important concern since it is associated with lower clinical responses and more adverse events. Biosimilars of Infliximab (e.g., CT-P13, SB2), one of the most immunogenic antibodies against TNF-α, have recently entered the market with the same indications to the innovator drug and are of use in clinical practice.[1] According to previous clinical studies, anti-drug antibodies (ADA) directed against innovator Infliximab recognise and bind CT-P13, illustrating that these two treatments may have common immunodominant epitopes. The authors' aim was to determine whether the successive switches from innovator infliximab to a first, and then second, biosimilar infliximab increase the risk of immunogenicity during a 3-year observation period.

This study was a usual care study performed in the Rheumatology, Gastroenterology, and Internal Medicine departments of Cochin Hospital, Paris, France. The first switch from innovator infliximab to CT-P13 occurred in October/December 2015, and the second switch from CT-P13 to SB2 started in December 2017. The end of the observation period was December 2018. Immunogenicity was defined by the detection of positive ADA >10 ng/mL, at least at two consecutive time points.

The authors prospective cohort consisted of 265 patients on maintenance therapy with innovator infliximab (135 with axial spondyloarthritis, 64 with inflammatory bowel diseases, 31 with rheumatoid arthritis, 21 with psoriatic arthritis, 8 with uveitis, and 6 with other chronic inflammatory diseases) who switched to CT-P13. Following this, 140 patients switched to SB2, 26 remained treated with CT-P13, and innovator infliximab was re-established in 55 patients. 30 patients (16 females) had positive ADA at baseline (point prevalence: 11.3%), before the switch to CT-P13. These patients were more likely to have a BMI >30 (45% versus 17%, p<0.001) and received less innovator infliximab infusions (28±20 versus 40±25 infusions, p=0.012) than patients without ADA. Among the 235 patients with no ADA at baseline, 20 patients developed ADA during the observation period, corresponding to a rate of 3 for 100 patient years. The mean time to positive ADA detection was 21.19±13.70 months (range: 1–37 months). Kaplan Meyer analysis, illustrating immunogenicity-free survival, showed no influence by the number of biosimilars infliximab received on immunogenicity. Among the 20 patients with positive ADA, 4 were back to innovator infliximab at the time of ADA detection. Positive ADA were detected in 10 patients during exposition to CT-P13, and 6 during exposition to SB2. The risk of treatment discontinuation was significantly higher in patients with positive ADA at baseline or during follow-up compared to patients without ADA ([HR: 2.27; 95% confidence interval: 1.33–3.89]). No predictive factor of immunogenicity was identified (including type of disease, age, sex, BMI, or concomitant disease-modifying antirheumatic drug intake). The retention rate of biosimilar infliximab was 58% (154/265) at the end of the observation period, including 131 patients treated with SB2 and 23 who remained treated with CT-P13.

In this usual care study with a 3-year observation period, the development of immunogenicity was low (3 for 100 patient years) and not favoured by the switch to biosimilars infliximab. Thus, immunogenicity does not constitute a barrier to interchangeability between biosimilars infliximab in chronic inflammatory diseases.

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Immunometabolism in Rheumatic Disease: The Role in Pathogenesis and Implications for Treatment

EDITOR'S PICK

Our Editor's Pick for this eJournal is the review paper by Thomas McDonnell et al. exploring the potential of immunometabolism in the context of pathogenesis of, and treatment for, a range of rheumatic diseases. This cutting-edge research holds promise for patients across the world. We hope you enjoy reading it as much as we did.

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Abstract

Rheumatic diseases collectively are complex disorders, often with multifactorial origins ranging from genetic risk factors to viral triggers. In many cases, the exact pathogenic mechanisms are poorly understood. Treatment response is often difficult to predict, and significant research is currently being undertaken to investigate new avenues for potential novel therapies. Immunometabolism, the study of the interface between immunological and metabolic processes, represents one such avenue at the forefront of this research and links cellular metabolism with the various changes in immunophenotypes observed across a variety of rheumatic disorders. Abnormal mitochondrial function and dysregulation of energy metabolism has been proposed as a potential mechanism for

the pathogenesis of systemic lupus erythematosus, inflammatory arthritis, and vasculitis. Furthermore, various metabolomic and amino acid changes have been observed across rheumatic diseases during activation of the immune and inflammatory response, thus representing an attractive prospect for medication development. In this review, the authors focus on immunometabolism in rheumatic disease, looking at mitochondrial dysfunction, fatty acid metabolism, and protein and amino acid changes across the disease spectrum. In particular, the authors evaluate the implications for the understanding of disease pathogenesis and explore the potential for immunometabolic intervention as a means of treatment.

INTRODUCTION

The field of immunometabolism is a rapidly expanding area of research that centres around understanding the interrelationship between immunological and metabolic processes.[1] Activation of the immune system is a dynamic process that requires significant immune metabolic reprogramming to induce and maintain proliferation of immune cells, as well as activation and engagement of effector cellular function.[2] Immunometabolism encompasses the roles of glycolytic and mitochondrial-derived energy metabolism, regulation of fatty acid oxidation and lipid synthesis, and protein kinase and amino acid metabolism.[3] A summary of the key immune cell metabolic pathways is highlighted in Figure 1.

In recent years, significant research has shed new light on the pathogenesis of various diseases with abnormal immunometabolism, including the development of atherosclerosis,[4,5] diabetes,[6,7] multiple sclerosis (MS),[8] and malignancy.[9]

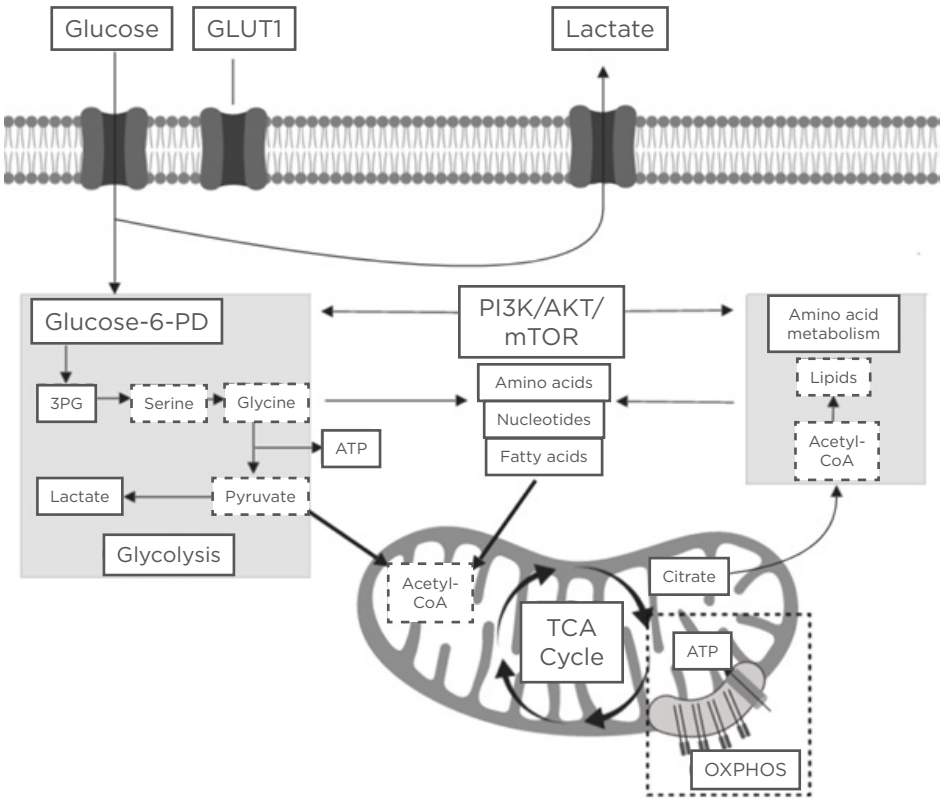

Figure 1: Summary of the key immune cell metabolic pathways.

Intracellular metabolism includes the generation of adenosine triphosphate through conversion of glucose to pyruvate via glycolysis and oxidative phosphorylation on the inner mitochondrial membrane electron transport chain.

3PG: 3-phosphoglycerate; Acetyl-CoA: acetyl coenzyme A; ATP: adenosine triphosphate; Glucose-6-PD: glucose-6-phosphate dehydrogenase; GLUT1: glucose transporter 1; mTOR: mammalian target of rapamycin; OXPHOS: oxidative phosphorylation; PI3K: phosphoinositide 3-kinase; TCA: tricarboxylic acid.

This has resulted in further research investigating the potential to alter the immunological–metabolic interface, which may represent a possible novel route towards new therapeutic targets.

Autoimmune rheumatic diseases are associated with activation of both the innate and adaptive immune system and results in the generation of autoantibodies and pro-inflammatory cytokines. This heterogenous group of disorders are typically characterised by a number of shared pathological mechanisms with a variety of different immunometabolic pathways implicated.

In this review, the authors describe the role of metabolic pathways during immune activation, evaluate the latest evidence supporting the role of changes in immunometabolism in various rheumatic diseases, and consider how this may lead to potential novel future therapeutic options.

GLYCOLYSIS, MITOCHONDRIA, AND ENERGY METABOLISM

Cellular metabolism is dependent upon two key metabolic pathways that are required to produce energy in the form of adenosine triphosphate (ATP): glycolysis and oxidative phosphorylation. In health, glycolysis is the metabolic pathway that converts glucose to pyruvate and hydrogen ions, which are essential for ATP generation. In the context of immune cell activation, metabolic reprogramming in glycolysis pathways are required for the induction and maintenance of cellular proliferation. Macrophages activated by lipopolysaccharide (LPS) have been demonstrated to switch their core metabolism to the glycolysis pathways. However, this change in metabolism pathways has been associated with an accumulation of a number of Kreb cycle intermediates, such as succinate, which stimulates IL-1β production and may induce a pro-inflammatory state.[10] Furthermore, metabolites, including fumarate and itaconate, have been implicated in this adaptive immune response.[11,12]

In the pathogenesis of autoimmune rheumatic diseases, glycolytic pathways have been studied in the context of autoreactive T cells in systemic lupus erythematosus (SLE), which are dependent upon glycolysis for early inflammatory effector functions. The activity of calcium/calmodulin-dependent protein kinase 4 has been suggested to be responsible for glycolytic pathways and, in turn, contributes to aberrant expression of the GLUT1 receptor in active SLE.[13] Yin et al.[14] previously demonstrated that by normalising T cell metabolism through inhibition of glycolysis with 2-deoxy-d-glucose, interferon-γ production in a murine SLE model was reduced. Whilst glycolysis has been implicated in the initial immune response, T cells that become chronically activated predominantly generate ATP from mitochondrial oxidative phosphorylation rather than glycolysis.[15]

In comparison to glycolytic energy metabolism, mitochondria produce ATP through oxidative phosphorylation using oxygen and nutrients, which is driven via an electrochemical gradient along the inner mitochondrial membrane. Mitochondria also represent the major source of reactive oxygen species (ROS) generation. A number of studies have observed that mitochondria can be potent activators of the immune-mediated inflammatory response.[16,17] In recent years, the study of mitochondria dysfunction, altered bioenergetic conditions, and ROS production have been investigated in the pathogenesis of a number of rheumatic diseases.

Mitochondria contain their own genetic material in the form of mitochondrial DNA (mtDNA) and this has also been implicated in the pathogenesis of various rheumatic diseases. Impaired energy metabolism can induce mitochondrial hypoxia, which has been shown to cause point mutations in mtDNA taken from the synovial tissue of patients with inflammatory arthritis. Further research showed the addition of antioxidants (in this case N-acetylcysteine [NAC]) rescue these mutations.[18] In addition, effective treatment with anti-TNF-alpha therapy has been demonstrated to reverse these mtDNA mutations.[19] Mitochondrial dysfunction results in damage to the structure of the organelle and ultimately in the release of mitochondrial genetic material from the cell into the microenvironment. This circulating cell free mtDNA can be detected in plasma and has been implicated in the pathogenesis of granulomatosis with polyangiitis (GPA), in which levels of mtDNA were found to be significantly elevated in those who were untreated, suggesting this may be a potentially novel biomarker.[20]

There is growing evidence from a number of studies supporting the role of abnormal mitochondrial function in the pathogenesis of

osteoarthritis (OA). OA chondrocytes stimulated by IL-1β have been noted to demonstrate high levels of ROS generation and mitochondrial membrane damage, which has been associated with a higher incidence of apoptosis.[21] Rheumatoid arthritis (RA) synovial fibroblasts have also demonstrated significant mitochondrial dysfunction and abnormal autophagy, which has also been seen in chondrocytes derived from patients with OA.[22,23]

The role of oxidative stress in the pathogenesis of SLE is well described,[24] however, the implications for mitochondrial dysfunction resulting in ROS production in the pathogenesis of the disease is a more recent area of interest.[25] Mitochondrial electron transport chain complex one has been reported as the main source of oxidative stress in peripheral lymphocytes in SLE. Furthermore, it was noted that NAC inhibited ROS production and proposed that this may be of possible therapeutic benefit.[26] Mitochondrial ROS have also been found to induce the formation of neutrophil extracellular traps (NET) through NETosis,[27] which has been implicated in the development of various autoimmune rheumatic disorders. A study by Lood et al.[27] found that mitochondria-derived ROS are essential for the induction of maximal NETosis in SLE. The authors also noted that inhibition of ROS formation *in vivo* resulted in a reduction in both type I interferon signature and disease severity in murine models. It was concluded that both NET and pro-inflammatory oxidised mtDNA play a key role in the pathogenesis of SLE.[27] Figure 2 summarises the ways in which mitochondrial dysfunction can result in ROS generation, NETosis, and the release of mtDNA. Previous animal studies have also implicated NETosis in the development of antibody-mediated thrombosis in antiphospholipid syndrome.[28,29]

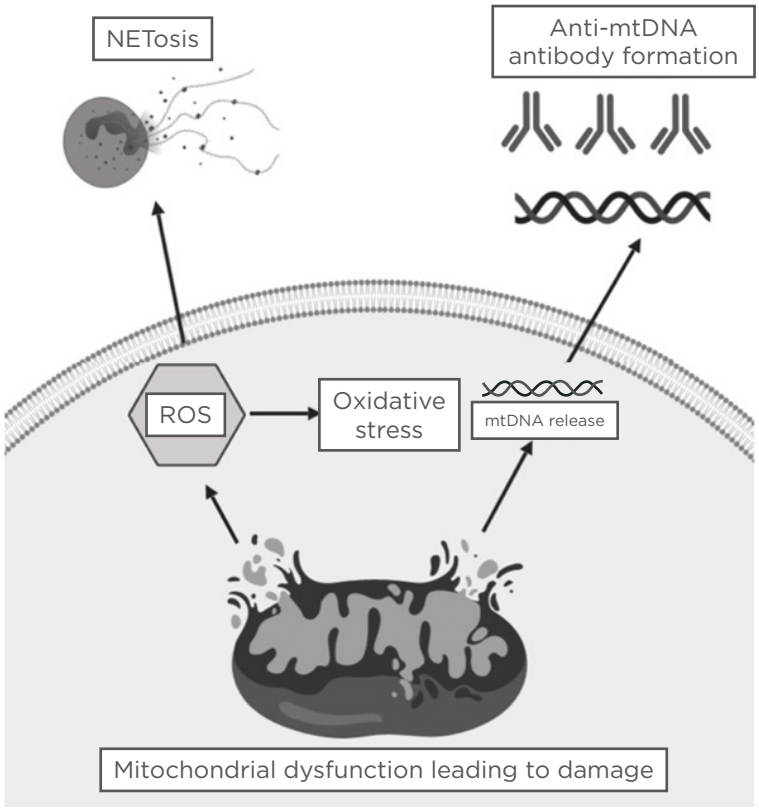

Figure 2: Summary of how mitochondrial dysfunction can result in reactive oxygen species generation, NETosis, and the release of mitochondrial DNA.

Mitochondrial dysfunction can induce damage to the outer mitochondrial membrane, which in turn can lead to the generation of reactive oxygen species and induce oxidative stress. Significant mitochondrial damage can result in mitochondrial DNA release, and, in turn, this circulating antigenic mitochondrial DNA may result in the formation of autoantibodies directed against mitochondrial genetic content.

mtDNA: mitochondrial DNA; ROS: reactive oxygen species.

Mitochondrial oxygen consumption was also noted to be elevated in the liver of 4-week-old lupus-prone mice, which led to the formation of anti-phospholipid antibodies prior to the onset of the disease phenotype. Furthermore, this was observed to be corrected with the addition of rapamycin,[30] a drug that targets and modulates autophagy pathways.

LIPID METABOLISM

Lipids are a critical aspect of metabolism, playing fundamental roles in cell membrane composition, membrane receptor signalling, and energy storage. The key lipids for cellular function include cholesterol, phospholipids, fatty acids, triglycerides, and glycosphingolipids (GSL). Lipid metabolism is implicated in a wide range of diseases including cardiovascular disease (CVD) and nonalcoholic fatty liver disease; however, more recent studies have shown a significant role for lipids in regulating inflammation and driving autoimmune diseases.[31-33]

Lipid metabolism is used in different ways depending on the immune cell. For example, regulatory T cells (Treg) use lipids for their anti-inflammatory functions through beta-oxidation in the mitochondria and generate ATP through oxidative phosphorylation, whereas effector T cells depend more highly on glycolytic over lipid mediated processes for the growth and proliferation necessary for their functions.[31] Lipids also play a significant role in the immune cell membrane in signalling platforms called lipid rafts.[32,33] These comprise signalling proteins, GSL, and cholesterol, which together mediate T cell and B cell receptor signalling through co-receptor recruitment to the raft.

CVD is a major complication of autoimmune diseases and this is largely due to prolonged inflammation and dyslipidaemia.[34] Dyslipidaemia broadly relates to the disrupted balance between low-density and high-density lipoproteins (LDL and HDL), which are pro-atherogenic and anti-atherogenic, respectively. Lipoproteins are responsible for transporting processed lipids, such as cholesterol and triglycerides, to HDL and from LDL in the liver.[35] SLE is a common example of an autoimmune disease heavily influenced by dyslipidaemia, and CVD has been shown to be the leading cause of mortality for SLE,[36,37] largely due to atherosclerosis. During atherosclerosis, macrophages take up the oxidised form of LDL in arteries, eventually resulting in macrophage foam cell formation and the formation of fatty lesions in the arterial wall. Rupture of the vessel wall can occur with excessive build-up of these fatty lesions, resulting in the recruitment of platelets, thus leading to narrowing of the arterial lumen.[38] It has also recently been shown that lipoproteins can control the balance of lipids in the immune cell membrane, thus controlling inflammation, another key driver of atherosclerosis.[39] In addition, lipid rafts have also been shown to be disrupted in SLE.[32,40] Jury et al.[41,42] showed an increase in cholesterol and GSL at the membrane to increased T cell receptor signalling at lipid rafts, and that a therapeutic intervention of GSL synthesis can normalise this signalling and reduce inflammation. Cholesterol is known to be involved in T cell activation,[43] thus it is another metabolic target for therapeutic agents, such as statins. Altered lipid rafts have also been shown to impact B cell receptor signalling in SLE.[44] Cholesterol has also been found to play a number of roles in the activated immune response. In autoimmunity, cholesterol metabolism has been implicated in the production of IFN-γ and immune complexes,[45] which have a significant role in the pathogenesis of a number of rheumatic conditions.

Similarly, despite being a disease associated with inflammation of the joints, comorbid conditions in RA have also been related to dyslipidaemia and CVD;[46] however, data is conflicting.[47] This is again likely to relate to the generalised effect of lipid metabolism and inflammation on early atherosclerosis in RA.[34] Active RA patients have been shown to have increased circulating HDL-cholesterol, and one study has demonstrated that this is also the case for untreated patients.[48] In addition, a separate study showed that smaller sizes of LDL and HDL, commonly shown to have more pro and anti-atherogenic effects respectively than their larger counterparts, were increased and decreased in the serum of RA patients, respectively.[49,50]

Current treatments for rheumatic disorders have been shown to influence lipid metabolism. An example in SLE is the use of hydroxychloroquine (an antimalarial agent), which has been shown to reduce levels of circulating LDL.[51] In contrast, the prolonged use of corticosteroids in SLE is

associated with driving further dyslipidaemia, despite its preferential effects on inflammation.[52,53] In addition, RA patients treated with glucocorticoids display increased levels of HDL.[54] Regarding lipid modification therapy, high dose statins (80 mg/day) are currently being trialled as a new therapy for patients with MS and the Phase II trial showed reduced rates of brain atrophy and disability progression in patients with secondary progressive disease.[55,56] In addition, RA patients treated with statins have shown improvements in erythrocyte sedimentation rate and C-reactive protein compared to patients on conventional standard of care therapy after 6 months of follow-up.[57] However, evidence that statins are beneficial in SLE patients, in terms of reducing cardiovascular risk and/or inflammation, is mixed. Some smaller studies have shown a beneficial effect;[58-61] however, the Lupus Atherosclerosis Prevention Study[62] and Atherosclerosis Prevention in Paediatric Lupus Erythematosus study[63] did not identify any beneficial effects of statins on disease activity or CVD risk measurements. Follow-up analysis has identified that patients with higher baseline C-reactive protein did, however, have improved CVD risk measures following the trial.[64,65] Thus, the success of future trials may depend on correct stratification of patients based on lipid profile and improved suitability of primary outcome measures.

Lipid metabolism is a key player in autoimmunity, and the therapeutic targeting of specific pathways holds promise for dual mediation of inflammation and CVD. The pathways that need to be targeted and the impact of these physiologically will need to be carefully considered, including the differential role of lipid metabolism across immune cell subsets. Further studies are required, but this opens the possibility of modulating diet to influence lipid metabolism as a potential treatment for autoimmune disease.

PROTEIN KINASE AND AMINO ACID METABOLISM

Proteins, peptides, and amino acids play an important role in immunometabolism in both health and disease, particularly with their effects on T cell differentiation and function. An imbalance between the pro-inflammatory T helper cell subsets, Th1 and Th17 cells, and anti-inflammatory Foxp3+ Treg, with the subsequent loss of self-tolerance, is thought to contribute to autoimmune disease.[66,67] Normally T cell differentiation into various cell subsets relies on the activation of the mTOR, a serine-threonine protein kinase that is present in two different complexes: mTORC1 and mTORC2.[68] It also helps maintain cell homeostasis by regulating metabolic signals and nutrient availability to drive genetic programmes involved in cell growth, activation, energy use, proliferation, and survival.[68-71] Through sensing cell energy status and the available metabolites, mTOR is capable of altering cellular activity.[68] mTORC1 activation alters T cell metabolism to provide the essential constituents required for Th1 and Th17 cell proliferation and differentiation; however, this signalling is also necessary for the suppressive function of Treg.[71]

In patients with SLE, mTORC1 activation occurs in CD4+ T cells.[69] This activation of mTORC1 may be driven by mitochondrial dysfunction secondary to the depletion of the tripeptide glutathione;[72] through hyperactivation of the pentose phosphate pathway and increased transaldolase activity;[70,73] or by a rise in the tryptophan metabolite kynurenine, which has immunomodulatory functions.[70,74] In rare cases, genetic activation of mTORC1 is possible.[70,75] mTORC1 activation may also represent a biomarker of autoimmune inflammation[68,69] and has been implicated in the pathogenesis of SLE in several ways. For example, activation has been detected after an increase in glycolysis and suppression of autophagy (including mitophagy) with subsequent mitochondrial dysfunction.[70] T cell necrosis, decrease in Treg populations, and an increase in pro-inflammatory Th17 and double-negative (CD4-CD8-) T cells[76,77] have also been observed. Double-negative T cells then in turn stimulate B cells to produce autoantibodies in SLE.[77]

Similarly in RA, there are metabolic interactions between enzymatic proteins in T cells, which are believed to play a key role in chronic inflammation underlying the disease.[78] T cells in RA are chronically activated, and thus undergo metabolic reprogramming, ultimately existing in a state of energy deprivation.[78] In early RA, this process occurs in lymphoid organs, with reduced activity of the enzyme 6-phosphofructo-2-

kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) in CD4+ T cells.[78,79] PFKFB3 is an enzyme that normally produces fructose 2,6-bisphosphate, which, in turn, activates the rate limiting enzyme in glycolysis, phosphofructokinase 1.[67,78] Reduced PFKFB3 activity results in a decrease in glycolysis, lower pyruvate and ATP levels, and shunting of glucose into the pentose phosphate pathway.[78,79] These T cells are predisposed to apoptosis and fail to induce autophagy, a process normally required for cells to recycle their internal biosynthetic precursors for energy generation.[78]

While shunting to the pentose phosphate pathway allows T cells to produce biosynthetic precursors required for clonal expansion, it has significant metabolic and functional consequences in RA.[67] Higher levels of nicotinamide adenine dinucleotide phosphate (NADPH) and reduced glutathione are produced, which neutralises ROS.[67] ROS normally act as messengers required for appropriate T cell activation, proliferation, migration, and apoptosis via oxidant signalling.[67,78,79] As a result of the depletion of ROS, oxidation-dependent cell signalling becomes dysregulated and there is insufficient activation of the cell cycle kinase ATM.[67] Thus, T cells become hyperproliferative and favour differentiation into pro-inflammatory Th1 and Th17 cell lineages.[67,79] In the later stages of RA, T cells invade peripheral tissues, such as synovial joints, interacting with B cells, plasma cells, antigen presenting cells, and tissue resident cells to create a lymphoid structure.[67,80] This lymphoid structure has hypermetabolic activity with immune cells continuing to release metabolites that promote inflammation in the surrounding synovial tissue.[67]

Increased understanding of these pathways could lead to more precise treatment of autoimmune rheumatic diseases because specific metabolic pathways could potentially be targeted to modify an immune cell response.[81] For example, both rapamycin (also known as sirolimus) and NAC inhibit mTORC1 and decrease disease activity in SLE patients.[72,82-84] A recent single-arm, open-label Phase I/II trial of 43 patients with treatment resistant and/or treatment intolerant SLE, found that disease activity improved following 12 months of sirolimus, particularly in those with mucocutaneous and musculoskeletal symptoms.[84] Sirolimus decreased IL-4 and IL-17 expression by pro-inflammatory double-negative and CD4+ T cells and upregulated Treg.[84] Unfortunately, the benefits of sirolimus are counterbalanced by commonly observed side effects including infection, hyperlipidaemia, and hyperglycaemia,[68,85] which is a concern in SLE because infections and CVD contribute greatly to mortality.[86] In comparison, NAC has few side effects[72] and the rationale behind its use is based on studies suggesting that both oxidative stress and reduced glutathione play a key role in the pathogenesis of SLE via abnormal T cell activation.[87,88] As well as inhibiting mTORC1, NAC reverses glutathione depletion, reduces double-negative T cell proliferation, and upregulates Treg.[72] Larger randomised controlled trials are required to further evaluate the effectiveness of sirolimus and NAC in SLE and other autoimmune rheumatic disorders characterised by abnormal mTOR activation.

CONCLUSION

In conclusion, recent advances in the understanding of the role of abnormal immunometabolism have shed new light on the pathogenesis of a number of rheumatic diseases. Similarly, research into lipid metabolism is revealing the ways in which rheumatic diseases are associated with non-traditional mechanisms of CVD. Understanding these complex interactions between metabolism and inflammation raises exciting opportunities to develop new innovative treatment options. For example, there is the possibility of using a variety of novel therapeutic agents including antioxidants (such as NAC) or even dietary modification (as a means of changing lipid profile) to ultimately improve disease activity and reducing symptoms in the future.

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Postmenopausal Osteoporosis: A Mini Review

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Abstract

Postmenopausal osteoporosis is an oestrogen deficiency-induced, systemic skeletal disease that affects the quality of life of patients once severe complications develop. The imbalance in osteoclastogenesis and osteoblastogenesis is the crucial pathological basis of osteoporosis and it is affected by classical pathways, epigenetic regulation, post-transcriptional regulation, oxidative stress-mediated signalling, and gut microbiotas. New methods to manage postmenopausal osteoporosis are essential and urgent. Dual-energy X-ray absorptiometry derived bone mineral density is acknowledged as the gold standard for osteoporosis diagnosis, and FRAX®, along with other clinical risk factors, has been used for osteoporotic fracture assessment. Novel serum biomarkers, such as circulating microRNA, are emerging and showing potential for diagnosing osteoporosis and estimating fracture risk. A major aim of osteoporosis diagnosis is to clarify the origins of the disease, clarify the functions of biomarkers and their dynamic changes responding to therapy, and develop a novel diagnostic strategy in combination with current methods. Traditional therapeutics,

including bisphosphonates, denosumab, oestrogen replacement, and teriparatide, have been used in osteoporosis therapy for a long time. Some severe side effects have resulted in therapy discontinuation; however, the incidence of adverse reactions is quite low. Developing novel treatments for osteoporosis using mesenchymal stem cells or Chinese medicinal herb-based therapy is of increasing interest to researchers, based on their improved safety, efficiency, and cost performance. Improvements in both diagnostic and therapeutic strategies may contribute to personalised management of osteoporosis.

EPIDEMIOLOGY

Osteoporosis is a systemic skeletal disease characterised by microarchitectural deterioration and high fragility of bone tissue, resulting in low bone mineral density (BMD) and poor bone quality, generally ascribable to oestrogen deficiency or ageing.[1] Osteoporosis is commonly regarded as a silent disease until it is complicated by systemic pain, spine deformation, height reduction, and fragility fracture. Fragility, or osteoporotic, fracture is the most dangerous complication of osteoporosis. These fractures can occur following minor trauma, but they can also occur spontaneously.[1] In the skeletal system, the spine, hip, and distal forearm are the regions most susceptible to osteoporotic fractures. In the USA, >9.9 million people have been diagnosed with osteoporosis and 43.1 million people are in a state of osteopenia.[2,3] Among them, nearly 1.5 million patients experience fragility fractures each year.[2,3] In Europe, 27.6 million people are diagnosed as osteoporotic each year, with >3.5 million of them experiencing osteoporotic fractures each year.[3,4] Until 2006, approximately 69.4 million people >50 years old were estimated to have osteoporosis, and 2.1 million people had osteopenia in China.[5] According to an epidemiological investigation of the population of Beijing, the incidence of spine fracture was about 15% in women >50 years of age.[5] In addition, the incidence of hip fractures had sharply increased by 42% in men and 110% in women from 1990–1992 compared with 2002–2006.[5] Fragility fracture augments the disability and mortality of osteoporotic patients; for example, about 20% of fragility fracture patients died of various complications within 1 year of hip fracture, while about half of the survivors who sustained a hip fracture remained disabled.[5] All of the aforementioned factors impose a great socioeconomic burden worldwide. Since oestrogen deficiency represents the most common cause of osteoporosis, this article will concentrate on the topic of postmenopausal osteoporosis.

PATHOPHYSIOLOGY OF POSTMENOPAUSAL OSTEOPOROSIS

The critical role of oestrogen deficiency in the pathogenesis of osteoporosis is based on the fact that postmenopausal womenare at thehighest risk of developing the disease (Figure 1). The bone metabolism of postmenopausal women is characterised by high bone turnover, which is defined as coinstantaneous increase of bone resorption and bone formation.[6] However, bone resorption exceeds bone formation after menopause, leading to an imbalance of bone remodelling and a rapid net bone loss.[6] In the first 5 years after menopause, bone loss occurs drastically and primarily in cancellous bone, while in the later years the bone mass decreases more slowly and mainly affects cortical and trabecular bone space, a process that can last for >10 years.[7]

Under physiological conditions, continuous and harmonious bone remodelling is maintained by an organised sequence of bone resorption followed by bone formation, which is termed osteoclast–osteoblast coupling. This partnership develops in response to dual regulation of mechanical force and endocrine factors.[8] Corporation of calcium and type I collagen-based bone matrix is crucial for osteoblast-mediated bone formation, which is under the control of endocrine factors, especially oestrogen.[8] Oestrogen has a central role in normal physiological remodelling; oestrogen deficiency breaks the balance of osteoclastogenesis and osteoblastogenesis, resulting in progressive bone loss (Figure 1).

The oestrogen receptors (OR) ORα and ORβ have been detected in osteoblasts, osteoclasts, and osteocytes. The nuclear receptor, ORα, primarily regulates bone metabolism.[7]

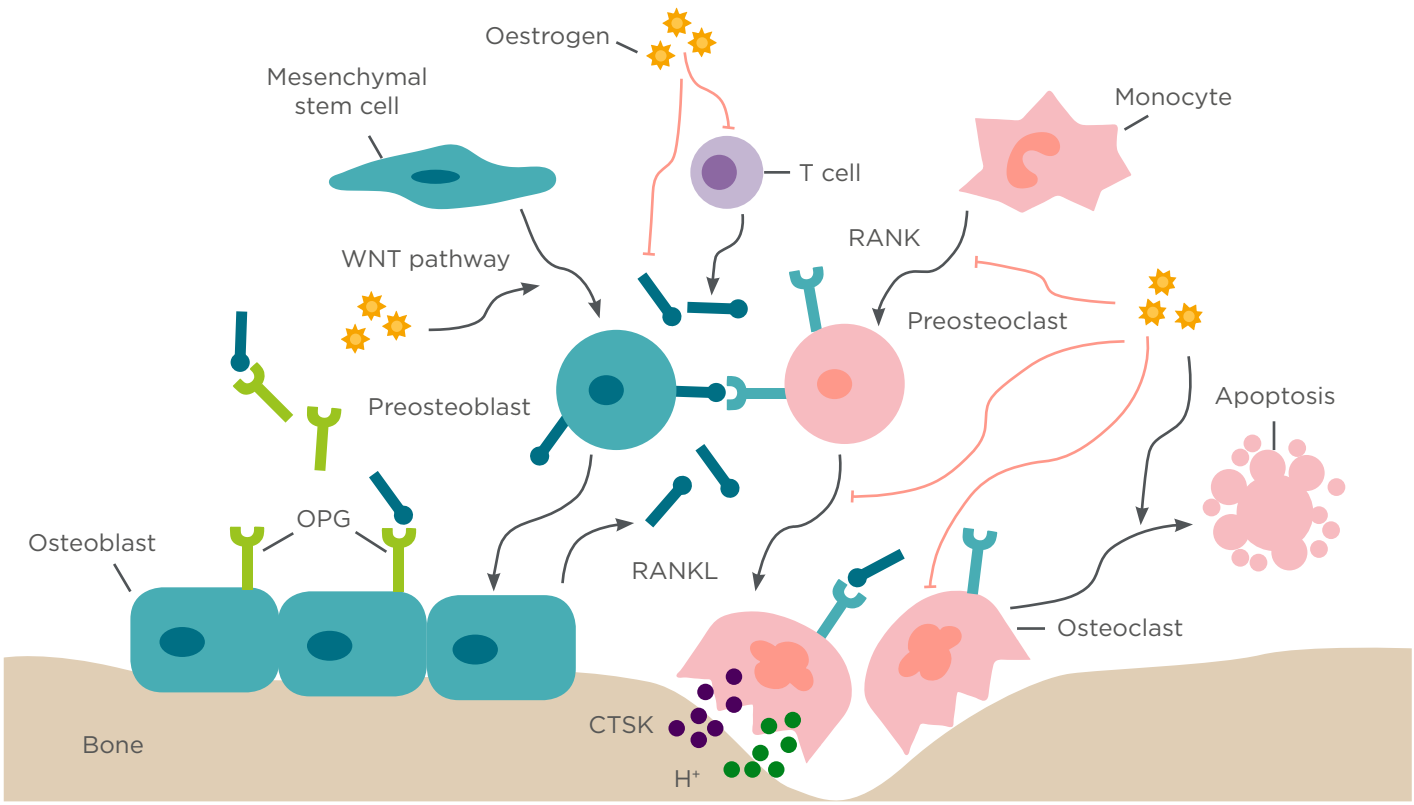

Figure 1: Bone remodelling.

Bone remodelling is based on a balance between osteoclastogenic bone resorption and osteoblastogenic bone formation, which is a crucial dynamic procedure during bone growth, development, and regeneration. Osteoblasts stem from mesenchymal stem cells and specifically generate extracellular bone matrix through the WNT signalling pathway. Osteoclasts originate from monocytic lineage and secrete bone resorptive factors through the RANK/RANKL/OPG signalling pathway. In addition, oestrogen also regulates bone remodelling by suppressing RANKL expression by T cells, mesenchymal stem cells, and osteoblasts.

CTSK: cathepsin K; OPG: osteoprotegerin; RANK: receptor activator of NFκB; RANKL: receptor activator of NFκB ligand.

Once bound to its ligand, ORα recruits coactivators or corepressors, and modulates transcription of oestrogen-responsive target genes accordingly. In addition, ORα can interact with transcriptional factors, including NFκB, and, as a result, downregulate its own downstream signals.[9] Osteoblasts and osteoclasts are involved in changes of cell fate in response to oestrogen deficiency, such as proliferation, differentiation, programmed cell death, and altered expression of target genes.

It is well known that osteoclast progenitors express receptor activator of NF κB (RANK), while osteoblasts express the ligand of RANK (RANKL) and the RANK antagonist osteoprotegerin (OPG). Physiologically, oestrogen regulates osteoclastogenesis via the core RANK/RANKL/OPG signalling pathway both *in vitro* and *in vivo*.[10,11] In the absence of oestrogen, enhanced crosstalk between RANKL and RANK provides the pivotal signal to promote osteoclast maturation and activation of osteoclast function.[12] Additionally, a reduced antagonism of RANKL by OPG also facilitates osteoclast formation and activation. Furthermore, an inflammatory microenvironment has been reported to be a crucial factor for oestrogen-mediated osteoclastogenesis regulation, for example, oestrogen maintains bone remodelling balance by enhancing osteoclasts apoptosis mediated by increased production of TGF-β.[13] However, in an oestrogen deficient environment, formation of osteoclasts is accelerated by increased osteoclastogenic proinflammatory cytokines, including IL-1, IL-6, IL-17, and TNF-α, which are negatively regulated by oestrogen.[14]

Bone morphogenetic proteins (BMP), TGF-β, insulin-like growth factor 1 receptor, and the WNT pathway are well-acknowledged, crucial signals involved in osteoblastogenesis regulation and bone formation, which are directly or indirectly regulated by oestrogen.[15] Oestrogen positively regulates osteoblastogenesis by stimulating the production of pro-osteoblastogenic factors, such as BMP, TGF-β, fibroblast growth factors, insulin-like growth factor 1, parathyroid hormone, and procollagen, resulting in the promotion of osteoblast formation, activity, and lifespan.[16]

Recently, pluripotent stem cells have been reported to be crucial in the regulation of the function and regeneration of local tissues. Mesenchymal stem cells (MSC) are commonly regarded as osteoblast precursors, which are critical for maintaining the balance of bone formation and resorption or the balance of bone formation and adipose formation.[17] Osteogenic differentiation of MSC is regulated by complex signalling. For instance, functional defects of the ALP, ERK, and FAS pathways;[18] epigenetic regulatory enzyme EZH2;[19] and GCN5[20] cause MSC dysfunction, sequential bone metabolism imbalance, and final osteoporosis. Disorders of MSC are largely considered the key pathological factor in the development of oestrogen deficiency-induced bone loss.[21] Oestrogen-deficiency induces chronic inflammation (via the promotion of TNFα, IFN-γ, IL-1, and IL-6 activity) that blocks MSC function and further initiates osteoporosis.[14] Moreover, during the osteoporotic process, microRNA (miRNA) play a significant role in the regulation of MSC function at the post-transcriptional level. Oestrogen deficiency alters MSC microRNA profile. microRNA, such as let-7, miR-17,[22] miR-26a,[23,24] miR-181a,[25] miR-705, and miR-3077,[26,27] can positively or negatively regulate osteogenic differentiation of MSC and osteoporosis development.

In addition, oxidative stress has been proposed as an alternative aetiology of osteoporosis for about two decades.[28] Elevation of reactive oxygen species following oestrogen deficiency enhances osteoblasts apoptosis and blocks the MSC survival and their functions.[29] Excessive reactive oxygen species in postmenopausal osteoporosis can largely be ascribed to the activation of the pro-oxidant enzyme system and deterioration of the enzymatic antioxidant system. NADPH oxidase 4 was observed to be provoked, meanwhile manganese superoxide dismutase and catalase were decreased during postmenopausal osteoporosis.[28,30,31] Rebalancing the pro-oxidant and antioxidant system effectively prevents oestrogen deficiency-induced bone loss.

Recently, the gut microbiota has been investigated as a crucial regulator of bone metabolic disorders in osteoporotic diseases. A germ-free mouse model, housed in a sterile environment, was used to understand the relationship between the microbiota, bone health, and systemic asepsis.[32] The germ-free mice showed higher bone density compared with mice raised in conventional conditions, suggesting that the microbiome was closely related to bone health.[32] Aberrant gut microbiota resulted in bone loss, whereas probiotic or antibiotic administration was demonstrated to rescue bone degeneration through modulating immune system, absorption of intestinal calcium in oestrogen deficiency-induced osteoporosis.[32] CD4+ T cells and inflammatory factors are commonly regarded as promoters of osteoclastogenesis during oestrogen deficiency.[33] A large decrease in CD4+ T cell populations and inflammatory factors was observed in the bone marrow following a treatment with probiotics.[32] However, the effects of the gut microbiota on bone health are complex and the precise mechanisms remain elusive.

DIAGNOSIS

Indications for Osteoporosis Diagnosis

Osteoporosis is a silent disease. Most osteoporotic patients do not realise they have the condition until its severe complications occur. Gynaecologists or family medicine physicians are usually the first healthcare providers who face the problem; therefore, indications for suspecting osteoporosis are necessary for them to decide whether the female patients should be sent for BMD testing. The US National Osteoporosis Foundation (NOF) has made the following recommendations, highlighting those most at risk 1) women >65 years of age, regardless of clinical risk factors; 2) younger postmenopausal women and women in the menopausal transition; 3) adults who have a fracture after 50 years of age; and 4) adults with a skeletal disease or taking a drug associated with low bone mass.

Traditional Diagnostic Regimen

BMD-derived, normalised, T score of the 1–4 lumbar vertebras, hip, or femoral neck is commonly accepted as the international gold standard for diagnosis of osteoporosis based on dual energy X-ray absorptiometry (DXA). T score is calculated as the formula: (BMD of candidate - peak BMD of population of the same sex)/standard deviation of peak BMD of population of the same sex. Candidates with T score ≥-1.0 are diagnosed as healthy; T scores between -2.5 and -1.0 are diagnosed as osteopenic; and T score ≤-2.5 are diagnosed as osteoporotic.[1]

BMD is the basis of future fracture risk assessment and, since the early 1990s, it has been well reported to be negatively related to the risk of future fracture incidence.[34] However, it is imprecise to evaluate fracture risk using BMD alone because of the fact that osteoporotic patients with a similar BMD sometimes show different fracture risks. Therefore, the World Health Organization (WHO) Fracture Risk Algorithm (FRAX®)[35] was developed based on femoral neck BMD and the clinical risk factors (current age, sex, a prior osteoporotic fracture, low BMI, rheumatoid arthritis, secondary causes of osteoporosis, parental history of hip fracture, smoker status, alcohol intake, and oral glucocorticoids) to estimate the 10-year probability of a major osteoporotic fracture.[35] However, this is not a rule, rather a clinical guideline; all management decisions should be made in consideration of clinical judgment on a case-by-case basis. Thus, consideration of the internal and external risk factors independent of BMD has been proposed by the WHO to improve the assessment strategy of osteoporotic fracture risk. Several risk factors have been identified, including lifestyle factors (low calcium supplement, excessive thinness, immobilisation, and falling), genetic diseases, endocrine disorders, hypogonadal states, rheumatologic and autoimmune diseases, gastrointestinal disorders, haematological diseases, neurological and musculoskeletal disorders, miscellaneous diseases, and pharmaceutical intervention.[1]

Serum and urine bone turnover biomarkers have been developed to estimate the status of bone formation and bone resorption, which are generally non-invasive and highly cost-effective. The most widely available markers include serum osteocalcin; bone-specific alkaline phosphatase; and total N-terminal propeptides of type I procollagen (tPINP), which are markers of bone formation; and urine or serum C-terminal cross-linking telopeptides of type I collagen (CTX-1) and tartrate-resistant acid phosphatase, which are markers of bone resorption.[1,36] Serum tPINP and CTX-1 are recommended for osteoporosis auxiliary diagnosis by the International Osteoporosis Foundation (IOF).[6] A correlation between osteoporotic status/fractures and bone turnover biomarkers independent of BMD has been reported in the osteoporotic population, including postmenopausal women.[6] Although the bone turnover markers have been developed for decades, their accuracy, specificity, sensitivity, and stability are still undefined in the clinical approach to osteoporosis management.

New Diagnostic Regimen

Recently, circulating microRNA have emerged as novel biomarkers for osteoporosis diagnosis and fracture prediction. Circulating microRNA are a type of small RNA that exist in body fluid, which are always specifically expressed *in vivo* and maintain stability for a long time *in vitro*.[37] Compared with traditional serum bone turnover markers, circulating microRNA have the advantages of higher sensitivity, stronger specificity, and better stability. It has been reported that dysregulated expression of circulating microRNA is always closely related to the pathological physiology of diseases.[38-40] Therefore, circulating microRNA has potential as a molecular diagnostic biomarker in the clinic.[41] According to research with a sample size of 120, serum miR-21 and miR-133a exhibited high potential as diagnostic markers for osteoporosis.[42] The researchers observed that serum miR-21 was downregulated among healthy participants, osteopenic patients, and osteoporotic patients; the opposite was true for miR-133a. In addition, miR-21, miR-23a, miR-24, miR-25, miR-100, miR-125b, miR-382-3p, miR-550a-5p, miR-122-5p, and miR-125-5p were also reported as potential predictors of osteoporotic fracture.[38,43,44] Moreover, a combinative panel of nine circulating microRNA (including miR-942-5p, miR-155-5p, miR-330-3p, miR-203a, and miR-181c-5p) showed a satisfactory predictive performance with an area under the curve of 0.97 to estimate osteoporotic fracture.[45]

However, the limitations of these biomarkers cannot not be neglected. The biomarkers are limited by a number of factors, such as easy degradation, temporal variability, the influence of food intake.[36] Despite these drawbacks, three additional points may yet come to influence the prospect of biomarkers application for osteoporosis: 1) clarify the origin of biomarkers and whether biomarkers function during osteoporosis development; 2) monitor dynamic changes to biomarkers to estimate the effects of anti-osteoporotic therapy; and 3) develop higher effective diagnostic strategy combined with traditional measures. Personalised diagnosis and treatment might be feasible in the future to manage osteoporosis through combined application of BMD, clinical risk factors, and disease-specific biomarkers.

THERAPEUTICS

Traditional Treatments

At present, the most common approach to preventing and treating osteoporosis is osteoclast inhibition. Several antiresorptive pharmaceuticals approved by the U.S. Food and Drug Administration (FDA) have been applied to osteoporosis treatment. Bisphosphonates, including alendronate, ibandronate, risedronate, and zoledronic acid, are antiresorptive drugs, which specifically bind to hydroxyapatite in bone tissues and sequentially inhibit osteoclasts attachment to bone surface, and through the suppression of lysosomal enzyme, pyrophosphatase, and prostaglandin, among proteins, prevent bone resorption.[46] Bisphosphonates have been widely used; the drug group represents a great advance in the treatment of osteoporosis and prevention of fractures, with a reduction of about 50% in the risk of vertebral fractures, while the reduction of nonvertebral fracture has shown a very variable range.[47,48] However, several side effects associated with the use of bisphosphonates have been reported, such as gastrointestinal disorders, osteonecrosis of the jaw, eye inflammation, atypical femur fractures, and renal function impairment.[1] Consequently, the consensus is growing to recommend administering bisphosphonates at a low dose in weekly formulations, and the responses of BMD and bone turnover markers are no different compared to those of daily formulations.[49,50]

Denosumab is a monoclonal antibody with high specificity and affinity to the receptor activator of RANKL.[51] It showed a prominent efficacy on postmenopausal osteoporosis with an incidence reduction of facture by approximately 70%, 40%, and 20% in vertebral, hip, and non-vertebral fractures, respectively, over 3 years.[51] Additionally, denosumab has also been reported to improve BMD in men at high risk of fracture. However, an abstinence reaction with rapid increase of bone turnover markers has been observed when denosumab administration is stopped.[52,53] Furthermore, the incidence of fragility fractures was back to baseline during the off-treatment stage.[52,53] Therefore, alternative agents should be applied in systematic treatment in osteoporotic patients to prevent denosumab deprivation-related bone loss.

Oestrogen replacement is the symptomatic treatment of choice to rescue postmenopausal bone loss and to reduce the risk of osteoporotic fracture. The Woman's Health Initiative (WHI) indicated that the risk of central skeleton fractures was reduced by approximately 30% and peripheral skeleton osteoporotic fractures by around 20% with a 5-year oestrogen replacement therapy regimen.[1] However, the WHI also reported increased risks of cardio-cerebral vascular incident, invasive breast cancer, deep vein thrombosis, and pulmonary emboli after long-term use of oestrogen replacement therapy. Additionally, an abstinence reaction with steep bone loss follows oestrogen deprivation. These serious side effects result in low enthusiasm for oestrogen replacement application in osteoporosis therapy. Nevertheless, oestrogen replacement is still an option for postmenopausal women with a high risk of fracture.[54] In addition, a selective oestrogen receptor modulator, especially raloxifene, reduces the risk of prior vertebral fractures by about 55% and vertebral refractures by about 30% over 3 years, whereas it has no effect on nonvertebral fractures.[1] However, the safety of raloxifene is also a concern, with an increased risk of thromboembolic disease, stroke, hot flashes, and leg cramps.[1]

Teriparatide, also known as the N-terminal 34 amino acid of parathyroid hormone, activates bone resorption and bone formation simultaneously.[55] It reduces the risk of vertebral fractures and non-vertebral fragility fractures by about 65% or 50% in osteoporotic patients,

respectively.[1] However, it has been reported to cause side effects like hypercalcaemia, nausea, and dizziness in human studies, and even osteosarcoma in animal studies.[1]

Therefore, it is urgent to develop safer, more effective alternative with an improved cost-effectiveness for the management of osteoporosis in consideration of adverse events and long-term safety concerns in clinical use about current therapeutic strategies.

NEW TREATMENTS

Since functional defects in MSC is the crucial aetiology for osteoporosis development, researchers have tried to treat osteoporosis through local or target transplantation of normal MSC. A study showed that bone marrow injection of bone marrow-derived mesenchymal stem cells (BMMSC)-alginate hydrogel mixture significantly improved bone deposition, hardness, and volume of trabecular bone in oestrogen deficient rabbits.[56] Additionally, the cancellous bone mass of ovariectomised rats were increased after infusion of BMMSC into bone marrow.[57] BMMSC coupling LLP2A has also been reported to enhance bone formation and finally increase bone mineral density in both oestrogen deficiency-induced osteoporosis and age-related osteoporosis.[17] Moreover, BMMSC transplantation has also been applied to relieve MSC dysfunction-related osteodysplastic diseases. Multiple clinical trials indicated that BMMSC transplantation increased bone growth and quality, and decreased fracture incidence of patients with osteogenesis imperfecta.[58] MSC transplantation ameliorates osteoporosis not only by providing normal stem cells, but also the modulation of the host's microenvironment and improving osteogenic function of the host's MSC. Systemic administration of MSC promotes osteogenesis of BMMSC and finally rescues the osteoporotic bone loss in oestrogen deficiency,[59] glucocorticoid,[60] diabetes,[61] and systemic lupus erythematosus models.[62] In addition, local application of cell aggregates of MSC sharply decreased the incidence of femur osteoporotic fracture from 93.75% to 37.50% in ovariectomised rat models.[63] Furthermore, exosomes derived from normal MSC also exhibits satisfactory efficacy on osteoporosis treatment, which ascribes to signalling substances contained in exosomes like functional proteins, small RNA, and so on.[18] Thus, MSC based therapy is a promising candidate regimen for osteoporosis treatment.

In recent years, an increasing enthusiasm has been generated by the management of osteoporotic diseases with traditional Chinese medicine as novel alternatives because of fewer adverse events and the accumulated experience of thousands of years of medicinal use (Table 1).

Table 1: Research on Chinese medicinal herbs on postmenopausal osteoporosis.

Type	Scientific name	Total clinical trials	Cellular level	Molecular level (pathways)	Efficacy
Single herbs	*Herba epimedium*	37	Osteoblasts	ER, WNT, BMP, ERK, TGF-β, NOTCH, PI3K	Coprescription of *H. epimedium* and other therapeutics achieved an overall efficacy of 73% in the improvement of osteoporotic symptoms. *H. epimedium* contributed 4.1% of relative weight to ameliorate postmenopausal osteoporosis in the coprescriptional formula.[64]
			Osteoclasts	RANK/RANKL/OPG, TNF-α, FAS/FASL, IL-6	
	Rhizoma drynariae	6	Osteoblasts	ER, WNT, BMP, NOTCH	Flavonoids from *R. drynariae* were better than conventional therapeutics in augmenting BMD (weighted mean difference=0.14; 95% confidence interval: 0.11–0.16).[65]
			Osteoclasts	RANK/RANKL/OPG, FAS/FASL	
	Salvia miltiorrhiza	25	Osteoblasts	WNT, ERK	Coprescription of *S. miltiorrhiza* and other herbs improved primary osteoporosis with an overall efficacy of 85–96% in osteoporotic symptom improvement.[66]
			Osteoclasts	RANK/RANKL/OPG	

Table 1 continued.

Type	Scientific name	Total clinical trials	Cellular level	Molecular level (pathways)	Efficacy
Active ingredients	Saikosaponins	N/A	Osteoclasts	RANK/RANKL/OPG, TNF-α, IL-6, ERK	Saikosaponins suppressed osteoclastogenic differentiation of murine macrophage cell line RAW264.7 cells.[67]
	Echinacoside	N/A	Osteoclasts	RANK/RANKL/OPG, anti-oxidation	Echinacoside prevented bone loss in OVX-induced Sprague–Dawley rats.[68]
	Psoralen	N/A	Osteoblasts	BMP 2, 4 and SMAD 1,5,8	Psoralen promoted osteoblast differentiation with a dose-dependent manner *in vitro*.[69]
	Linarin	N/A	Osteoblasts	BMP, PKA	Linarin preserved the trabecular bone of OVX mice. In addition, it promoted osteoblastogenic differentiation of MC3T3 E1 cells.[70]
	Osthole	N/A	Osteoblasts	WNT, BMP	Osthole improved bone mass and quality in OVX rats. In addition, it also improved osteoblasts differentiation *in vitro*.[71]
	Baicalin	N/A	Osteoblasts	WNT	Baicalin stimulated osteoblastic differentiation *in vitro*.[72]
	Vanillic acid	N/A	Osteoblasts	ER, MAPK	Vanillic acid improved the proliferation and ALP activity of rat osteoblast-like UMR 106 cells.[73]
			Osteoclasts	RANK/RANKL/OPG	

ALP: alkaline phosphatase; BMD: bone mineral density; BMP: bone morphogenetic protein N/A: not applicable; OPG: osteoprotegerin; PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase; PKA: protein kinase A; RANK: receptor activator of NFκB; RANKL: receptor activator of NFκB ligand; TGFβ: transforming growth factor beta.

Chinese medicinal herbs containing multiple components usually exert their therapeutic effects on postmenopausal osteoporosis through complicated mechanisms. Multiple pathways have been revealed to rebalance osteoblastogenesis and osteoclastogenesis, including oestrogen receptor dependent, RANK/RANKL/OPG, BMP, Wnt/β-catenin, ERK, TGF-β, and Notch signalling pathways.[74,75] Apart from restoring the balance between osteoblastogenesis and osteoclastogenesis, Chinese medicinal herbs have also been founded to modulate the balance of adipocytes and osteoblasts, which is also critical to bone metabolism.[75] Moreover, many Chinese medicinal herbs have chemical structures or chemical groups similar to oestrogen. They exert oestrogen-like functions as well as immunoregulation and antioxidation, which have been indicated to ameliorate osteoporosis.[75] In addition, Chinese medicinal herbs and other natural small molecules, like melatonin,[59] rapamycin,[76] and licochalcone A,[63] have also been used in MSC pretreatment to improve MSC-based therapy in osteoporotic diseases. It seems feasible and valuable to develop novel therapeutics for osteoporosis therapy based on combined use of MSC and Chinese medicinal herbs.

THE FUTURE: GOAL-GUIDED TREATMENT

The current consensus is growing to manage osteoporosis, with the aim to approach target efficacy, such as target BMD or lowered fracture risk, which is termed as goal-guided treatment strategy. It is recommended to choose drugs based on the osteoporotic patient's characteristics and therapeutic features and adopt a corresponding method to monitor therapeutic effects. However, standard treatment goals have yet to be defined. Temporarily,

dynamics of BMD and bone turnover markers during the course have been proposed to guide when to pause or switch therapeutics. Apart from traditional managements, novel biomarkers and new medications might also contribute to treatment modification and further promote personalised diagnosis and therapy for osteoporosis. A synopsis of clinical management for postmenopausal osteoporosis are displayed in Table 2.

Table 2: Synopsis of clinical management for postmenopausal osteoporosis.

Process	Strategy
1. Risk estimation	Age, sex, prior osteoporotic fracture, low BMI, diet, rheumatoid arthritis, secondary causes of osteoporosis, parental history of hip fracture, current smoking, alcohol intake, and oral glucocorticoids.
2. Diagnosis	**Gold standard:** BMD testing by DXA (normalised as a T score): lumbar vertebrae, hip, or femoral neck. **Auxiliary diagnosis:** Serum and urine bone turnover biomarkers: OCN, BASP, tPINP, CTX-1, TRAcP. **New diagnosis:** Circulating microRNA: miR-21, miR-23a, miR-24, miR-25, miR-100, miR-122-5p, miR-125-5p, miR-125b, miR-133a, miR-155-5p, miR-181c-5p, miR-203a, miR-330-3p, miR-382-3p, miR-550a-5p, and miR-942-5p.
3. Treatment	**Traditional treatment:** Bisphosphonates: alendronate, ibandronate, risedronate, and zoledronic acid. Denosumab Oestrogen replacement Teriparatide **New treatment:** Stem cell-based therapy: mesenchymal stem cells Traditional Chinese medicine and other small molecules: *Herba epimedium, Rhizoma drynariae, Salvia miltiorrhiza*, saikosaponins, echinacoside, psoralen, linarin, osthole, baicalin, vanillic acid, licochalcone A, melatonin, and rapamycin.

BASP: serum bone-specific alkaline phosphatase; BMD: bone mineral density; CTX: carboxy-terminal collagen crosslinks; DXA: dual-energy x-ray absorptiometry; OCN: osteocalcin; tPINP: type 1 N-terminal peptide; TRAcP: tartrate-resistant acid phosphatase.

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Update on the Diagnosis and Anticoagulant Treatment of the Antiphospholipid Syndrome

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Abstract

Antiphospholipid syndrome (APS) is an acquired form of thrombophilia characterised by the presence of antiphospholipid antibodies and arterial/venous thrombosis or obstetric complications. Although antiphospholipid antibodies are reported in 1–5% of the general population, only a minority of these individuals will develop the clinical manifestations of APS. The typical expressions of APS are thrombotic events that can involve veins, arteries, or small vessels in any organ or tissue. Pregnancy morbidity refers mainly to early and late fetal loss, but pre-eclampsia, eclampsia, or placental insufficiency can also occur. Extra-criteria manifestations include thrombocytopenia, APS-associated nephropathy, valvular heart disease, neurological manifestations, and livedo reticularis. The diagnosis of APS is currently based on the Sydney criteria: i.e., meeting at least one clinical criterion (vascular thrombosis or pregnancy morbidity) and one laboratory criterion (lupus anticoagulant, anticardiolipin antibodies, or anti-β2 glycoprotein-I antibodies). Anticoagulation with unfractionated or low molecular weight heparin followed by vitamin K antagonist is the standard treatment for APS patients presenting with venous thromboembolism. There is not enough evidence regarding the use of the direct oral anticoagulants in this population. Patients presenting with arterial thrombosis may receive a combination of vitamin K antagonists and low-dose aspirin. In women with obstetrical APS, the combination of low molecular weight heparin and low-dose aspirin is usually prescribed to prevent pregnancy complications. The aim of this narrative review is to summarise the latest evidence on the diagnosis and antithrombotic treatment of APS.

INTRODUCTION

Antiphospholipid syndrome (APS) is an acquired form of thrombophilia with immune pathogenesis and is characterised by the presence of antiphospholipid antibodies (aPL) and clinical manifestations of arterial or venous thrombosis or obstetric complications. APS is sometimes known as Hughes syndrome, named after the author who first described a common pathogenic mechanism underlying recurrent venous thrombosis, cerebral diseases, and recurrent abortions in patients with systemic lupus erythematous (SLE).[1]

EPIDEMIOLOGY

Although aPL are reported in 1–5% of the general population,[2] only a minority of these individuals will develop the clinical manifestations of APS. The incidence of APS is approximately 5 new cases per 100,000 people per year, while the prevalence is 40–50 cases per 100,000 people.[3] The prevalence of aPL in patients with clinical events is higher: 13.5% in stroke, 11.0% in myocardial infarction, 9.5% in deep vein thrombosis, 6.0% in pregnancy morbidity, and 26.4% in women with recurrent early pregnancy loss.[4,5]

APS can occur without other conditions, known as primary APS, or can be associated with other autoimmune diseases, such as SLE or rheumatoid arthritis, which is known as secondary APS. The prevalence of aPL in SLE patients can reach 40%,[2] and 20–50% of these will develop thrombotic events.[6]

PATHOPHYSIOLOGY

aPL are autoantibodies directed against cell surface proteins bound to anionic membrane phospholipids. They are a heterogeneous group of autoantibodies, including lupus anticoagulant (LAC), anticardiolipin (aCL) antibodies, and anti-β2 glycoprotein-I (aβ2-GPI) antibodies.

The history of aPL dates back to the beginning of the 20th century, with the discovery of biological false-positive serological tests for syphilis, due to the interaction between aCL and cardiolipin used as a reagent in these assays.[7] LAC was first described in the 1950s, in patients with SLE and prolonged clotting time *in vitro*, hence the name lupus anticoagulant.[8] However, LAC can also be found in patients without SLE and it is known today as the paradox between the prolonged phospholipid-dependent coagulation tests *in vitro* and the hypercoagulable state *in vivo*.

The central role of antibodies against β2-GPI, a complement regulator and inhibitor of coagulation, was discovered in the 1990s,[7] and a specific immunoassay for aβ2-GPI was developed. β2-GPI is the key antigen for all aPL. β2-GPI is a cofactor for aCL to bind cardiolipin, and the aCL that recognise the β2-GPI (β2-GPI-dependent aCL) correlate more strongly with thrombosis and obstetric complications, compared to β2-GPI-independent aCL.[9] It was also demonstrated that LAC activity due to aβ2-GPI (β2-GPI-dependent LAC) is more correlated with thrombotic events than β2-GPI-independent LAC (such as LAC due to antiprothrombin antibodies).[9,10] Furthermore, the aβ2-GPI can be specific for different domains of the β2-GPI molecule, and those antibodies directed towards the domain I were shown to be more predictive of clinical events.[11]

The pathophysiology of APS is still not completely understood. The main triggers for aPL synthesis are infections, due to the molecular mimicry between protein components of the infectious agents and cell surface proteins, such as β2-GPI.[6] However, the presence of aPL alone (the 'first hit') is not sufficient to provoke a thrombotic event and a 'multi-hit' theory has been proposed, wherein other factors (such as infections, inflammatory diseases, surgery, immobility, and hormonal treatment) constitute the 'second hit' and drive the haemostatic balance towards thrombosis.[6,8] Several pathways have been hypothesised to explain the procoagulant state induced by aPL, including complement activation, activation of platelets and endothelial cells, interference with the natural anticoagulants (protein C and tissue factor pathway inhibitor), and inhibition of fibrinolysis.[8,12]

Regarding obstetrical complications, the apoptotic effect of aPL on trophoblast cells can explain the early pregnancy morbidity (recurrent miscarriages), while ischaemic placental dysfunction can explain the late pregnancy morbidity: pre-eclampsia, intrauterine growth restriction or death, premature birth, and stillbirth.[5]

CLINICAL MANIFESTATIONS

The typical manifestations of APS are thrombotic events that can involve veins, arteries, or small vessels in any organ or tissue. In the large cohort of 1,000 patients with APS enrolled in the Euro-Phospholipid Project,[13] the most common clinical presentation was venous thromboembolism (VTE): deep vein thrombosis (31.7%), superficial thrombophlebitis (9.1%), and pulmonary embolism (9.0%). Arterial thrombosis (ATE) were less frequent: stroke (13.1%), transient ischaemic attack (7.0%), and myocardial infarction (2.8%).[13]

During the evolution of APS, a number of unusual-site thromboses were also reported, including cerebral vein thrombosis, mesenteric ischaemia, Budd–Chiari syndrome, renal artery or vein thrombosis, arterial thrombosis of the upper or lower extremities, and retinal artery or vein thrombosis.[13,14]

Pregnancy morbidity refers mainly to early and late fetal loss, reported in 35.4% and 16.9% of pregnancies in APS women, respectively.[13] In the European Registry on Obstetric Antiphospholipid Syndrome, recurrent early miscarriage (53.8%) and late fetal loss (31.2%) were the most frequent obstetric complications.[15] Other possible obstetric complications are pre-eclampsia, (9.5%), eclampsia (4.4%), and abruption placentae (2.0%).[13]

Furthermore, there are other clinical manifestations of APS, known as extra-criteria manifestations, which are not included in the classification criteria,[16,17] but can be helpful to raise the suspicion of APS. The extra-criteria manifestations can be associated with thrombosis and pregnancy morbidity or can be isolated. Thrombocytopenia is reported in 20.0–46.0% of APS patients, is usually moderate (platelet count 50–100x10^3/mm^3), and is associated more with thrombosis as opposed to bleeding risk.[16,18] The APS-associated nephropathy is defined by the histopathologic finding of thrombotic microangiopathy, which can involve both arterioles and glomerular capillaries, and is closely correlated with kidney failure.[18] Valvular heart disease includes sterile valve vegetations, thickening, and dysfunction, can lead to heart failure, and may require heart valve replacement.[18] Several neurological manifestations have also been correlated with aPL, including chorea, myelitis, seizures, migraine, and cognitive impairment.[17] Livedo reticularis can be the presenting clinical manifestation in approximately 40% of APS patients;[19] this is a typical pattern of the skin, either mottled or reticular, with a colour ranging from reddish-blue to purple, and localised to the trunk, arms, or legs. The 'regular livedo reticularis' consists of regular unbroken circles, whereas the 'livedo racemosa' consists of irregular broken circles, and is also more generalised and irregularly distributed than the livedo reticularis.[16,19] The rare Sneddon's syndrome is the association of livedo, either reticularis or racemosa, and cerebrovascular events.[20] The relevance of extra-criteria manifestations is still debated.

Although they are not currently included in the APS classification criteria, a report from the Antiphospholipid Antibodies Task Force on Clinical Manifestations suggested there is moderate evidence to support the inclusion of APS-nephropathy, valvular heart lesions, and livedo reticularis.[18]

Finally, on rare occasions a catastrophic variant of APS (CAPS), also known as Asherson's syndrome,[21] can develop. The prevalence of CAPS is <1.0% of all patients with APS; it is a potentially life-threatening condition with very high mortality rates (40–50%).[22] CAPS is characterised by the rapid development of extensive microvascular thrombosis, leading to multiorgan failure. Any organ can be affected, but CAPS typically involves the kidneys, lungs, and central nervous system. Precipitating factors have been recognised in 65% of cases, most commonly infections, surgery, malignancies, and hormonal stimuli, such as oral contraceptives or pregnancy.[22] The classification criteria for CAPS were established in 2002, and were defined as thrombosis in three or more organs, simultaneous development or development within a week, histopathological confirmation of small vessel occlusion, and laboratory confirmation of aPL (LAC and/or aCL, usually in high titre).[23] The diagnosis of 'definite CAPS' requires all four criteria, while 'probable CAPS' is diagnosed when the four criteria are not completely fulfilled or with different combinations of three criteria. Particular laboratory findings reported in the international CAPS Registry[24] include thrombocytopenia (67%), haemolytic anaemia (37%), schistocytes (22%), thrombotic microangiopathy (14%, defined as the association of thrombocytopenia, haemolysis, and schistocytes), and disseminated intravascular coagulation (11%, defined as the association of thrombocytopenia, increased D-dimer, and prothrombin time).

DIAGNOSIS

Diagnostic Criteria

The diagnosis of APS is currently based on Sydney criteria:[16] at least one clinical criterion (vascular thrombosis or pregnancy morbidity)

and one laboratory criterion (LAC, aCL, or aβ2-GPI) should be met (Table 1). Vascular thrombosis can involve arteries, veins, or small vessels in any organ, and should be confirmed by appropriate imaging or histopathology. If histopathological confirmation is sought, thrombosis must be present without any sign of inflammation of the vascular wall. Superficial vein thrombosis is not included in the clinical criteria. Recurrent first trimester miscarriages are defined as ≥3 unexplained consecutive abortions before the 10th week of gestation, after having excluded maternal anatomic or hormonal abnormalities and maternal and paternal chromosomal abnormalities.[16]

Laboratory Tests

The presence of aPL should be confirmed by specific laboratory tests, for which the timing is crucial. Some groups argue that these tests should not be performed during the acute phase (the first 12 weeks) after a thrombotic event,[16] to avoid false-positive results. However, these tests could give an indication of the actual diagnosis when it matters, such as in those patients with the catastrophic type of APS. In any case, a positive laboratory test should always be confirmed at least 12 weeks apart, to exclude the transient presence of aPL, which is common after infectious diseases.[16,25,26] The diagnosis of APS should not be made if the positive laboratory test occurs >5 years after the clinical event.[16] Finally, the LAC tests are best postponed until after discontinuation of anticoagulant treatment, to avoid interference in the prolongation of the basal clotting time.[16] Practical suggestions have been reported: delay for 1–2 weeks after discontinuation of vitamin K antagonists (VKA) or when the international normalised ratio (INR) is <1.5; if bridging with low molecular weight heparin (LMWH), delay for at least 12 hours after the last dose; wait until after discontinuation of the direct oral anticoagulants (DOAC).[27] In those patients who are treated with a DOAC, there is another way to remove the anticoagulant effect and allow testing, involving the addition of DOAC-Stop® to the plasma sample.[28]

The LAC should be tested according to the guidelines of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies of the International Society on Thrombosis and Haemostasis.[25,26] The tests should be expressed as a ratio between the coagulation time of the patient plasma and normal pooled plasma, and a multistep procedure of screening, mixing, and confirmation tests is usually recommended. Since no single test has enough sensitivity to account for antibodies' heterogeneity, two phospholipid dependent clotting assays should be performed as screening tests to exclude the presence of LAC.[16,26] The Dilute Russell viper venom time is the first test of choice, because of its specificity for clinically significant antibodies.

Table 1: Classification criteria for the antiphospholipid syndrome (Sydney criteria).

Clinical criteria	Venous thrombosis (e.g., deep vein thrombosis, pulmonary embolism, unusual site venous thromboembolism)
	Arterial thrombosis (e.g., coronary artery disease, transient cerebral ischaemia or stroke, peripheral artery disease)
	Obstetric complications: • Three or more unexplained consecutive spontaneous abortions <10th week of gestation. • One or more unexplained deaths of a morphologically normal fetus ≥10th week of gestation. • One or more premature births of a morphologically normal neonate <34th week of gestation due to eclampsia, severe pre-eclampsia, or placental insufficiency
Laboratory criteria	Lupus anticoagulant, detected according to international guidelines
	Anti-cardiolipin antibodies, IgG, or IgM isotype, at high titre (>99th percentile of normal controls)
	Anti-β2 glycoprotein-I antibodies, IgG, or IgM isotype, at high titre (>99th percentile of normal controls)

The second test should be a sensitive activated thromboplastin time, using silica as an activator, and low phospholipid concentration to emphasise the effect of the LAC by competition for the limited phospholipid-binding sites.[29] A positive screening test shows prolongation of the clotting time.[26] The mixing test is performed by adding normal pooled plasma to patient plasma with a 1:1 ratio, to differentiate among the possible causes of prolonged clotting time. While coagulation factor deficiencies are corrected by the mixing test, the presence of coagulation inhibitors (such as LAC) still result in a prolongation of the clotting time.[26] Finally, a confirmatory test is performed by increasing the concentration of phospholipid in the screening test, to overwhelm any aPL and demonstrate phospholipid dependence.[29] A positive confirmatory test shows normal clotting time.

The recent development of integrated tests, which can perform screening and confirmation tests in parallel just by varying the concentration of phospholipid, has reduced the number of mixing tests.[26] However, the role of the mixing test is still debated; while some authors acknowledge that it can introduce a dilution factor and generate false-negative results if the LAC is weak,[30] others argue that the mixing test still has a role when the other test results are borderline[29] or that skipping the mixing test might generate both false-negative and false-positive results.[31]

The aCL and aβ2-GPI are usually detected by enzyme-linked immunosorbent assays, but recently automated solid phase assays have also been developed.[25,32] Only IgG or IgM isotypes at high titre are considered positive, defined as antibodies levels above the 99th percentile of a cut-off established locally on a population of healthy volunteers.[25,32] IgG showed a strong association with the risk of thrombosis,[32] while IgM showed possible false-positive results in the presence of cryoglobulins and rheumatoid factor, especially when at low titre.[16]

Guidelines recommend that all three tests (LAC, aCL, and aβ2-GPI) should be performed on the same sample to characterise the patient antibodies profile.[25] The risk of clinical events increases in parallel with the number of positive tests and is especially high when all three tests are concomitantly positive, known as triple positivity. Furthermore, a recent study showed that 98% of patients with triple positivity and 84% with double positivity were confirmed at the 3-month follow-up, versus 40% with single positivity.[33]

Problems in APS diagnosis might arise from technical difficulties. Despite the efforts to standardise the laboratory diagnosis of aPL, the inter-laboratory variability in the detection of the LAC remains high.[34] Furthermore, kits for the detection of autoantibodies, especially aCL, produced by different manufacturers may provide different results, even when performed in the same laboratory.[35]

Non-Criteria Antiphospholipid Antibodies

Several other autoantibodies not included in the laboratory criteria have been recently identified in APS patients. They include IgA aPL isotypes (IgA aCL and IgA aβ2-GPI), antibodies against prothrombin (aPT) or phosphatidylserine/prothrombin complex (aPS/PT), and antibodies against the domain 1 of β2-GPI.[17] IgA isotypes could contribute to the identification of APS patients, but they are currently not considered a diagnostic marker for APS, the reason being that they often coexist with the IgG and IgM isotypes. Anti-prothrombin antibodies were recently reported as a risk factor for thrombotic events, especially aPS/PT.[36] Autoantibodies directed only against epitopes in the domain 1 of β2-GPI were more frequently detected in patients with triple-positivity and they were associated with a history of thrombosis.[37] The practical relevance of these non-criteria antiphospholipid antibodies is currently debated. However, there is recent evidence that they could be involved in APS pathogenesis and explain some of the seronegative APS.[17]

Patient Selection

Asymptomatic patients should not be routinely screened for aPL to avoid incidental findings of false-positive results, due to the poor specificity of these assays.[26,32] The appropriateness of searching for aPL is high in young (<50 years of age) patients with unprovoked VTE or unexplained ATE, unusual site VTE, thrombosis or pregnancy complications associated with autoimmune diseases, or late pregnancy loss.[26] The appropriateness is moderate in

young patients with provoked VTE, recurrent spontaneous early pregnancy loss, or unexplained prolonged activated thromboplastin time, and is low in elderly patients with VTE or ATE.[26]

PROGNOSIS

APS carries significant morbidity and mortality. Among the patients included in the Euro-Phospholipid project, mortality rates were 5.3% in the initial 5-year follow-up and 4.0% in the subsequent 5-year follow-up.[38] Thrombotic events (such as myocardial infarction, stroke, and pulmonary embolism) were the most common causes of death (36.5%), followed by sepsis (26.9%), malignancies (13.9%), and haemorrhages (10.7%). Furthermore, the most recent follow-up showed that, despite antithrombotic treatment, 24.8% of patients developed thrombosis and 8.3% had obstetric complications.[38]

Antibody profile is the major risk stratification tool. Patients with a single isolated positivity are at low risk of clinical manifestations of APS,[27] whereas patients with triple positivity showed the strongest association with thrombotic or obstetric events. In a cohort of 160 triple positive APS patients with a mean follow-up of 6 years, ATE or VTE occurred in approximately 34.0% of patients: 36 of 123 (29.3%) anticoagulated patients and 19 of 37 (51.4%) non-anticoagulated patients.[39] Among APS patients who suspended anticoagulant treatment for different reasons, 43.3% had recurrent thrombosis during a median follow-up of 4.3 years and triple positivity was a strong predictive factor for relapse.[40] Despite appropriate treatment, in triple-positive women, the likelihood of a live-birth neonate is only 30%, compared to approximately 80% in those with single LAC positivity.[41]

Furthermore, triple positivity in asymptomatic aPL carriers is associated with a considerable risk of developing a first thrombotic event.[42,43] It has been estimated that the annual rate of a first vascular event is 0.40% in normal subjects, 1.36% in single positivity aPL carriers, and 5.30% in triple positivity aPL carriers.[42] Another study reported that the annual rate of a first vascular event was 0.65% in single positivity aPL carriers and 1.27% in double or triple positivity aPL carriers.[43] In both studies, approximately a third of patients were receiving prophylactic low-dose aspirin, which was not associated with reduced risk of arterial or venous thrombotic events.[42,43]

A global APS score (GAPSS) was recently developed to predict the clinical manifestations of APS: thrombosis and pregnancy loss.[44] The GASPSS includes a number of variables: aCL (5 points), LAC (4 points), aβ2-GPI (4 points), anti-prothrombin/phosphatidylserine complex (3 points), hyperlipidaemia (3 points), and arterial hypertension (1 point). The adjusted GAPSS (aGAPSS) is a simplified version, which excludes the antibodies against prothrombin/phosphatidylserine, since they are not routinely tested and not included in the classification criteria for APS.[45] The GAPSS and aGAPSS have been validated in different populations, including patients with SLE or other systemic autoimmune diseases (to predict the first manifestations of APS) and in patients with primary or secondary APS (to predict recurrent events).[46]

TREATMENT

Anticoagulant Treatment

In APS patients presenting with VTE, the standard initial treatment involves unfractionated heparin (UFH) or LMWH, followed by VKA with INR target range 2.0–3.0.[30] This recommendation is based on the results of two randomised controlled trials (RCT) (Table 2) showing that a higher INR target range was not associated with a further reduction of recurrent thrombosis.[47,48] Considering the high risk of thrombosis recurrence after discontinuation,[49] anticoagulant treatment duration should be long-term for APS patients with unprovoked VTE, while the benefit of extended anticoagulation in APS patients with VTE provoked by a transient risk factor is still debated.[50]

Monitoring VKA can be difficult in APS patients. Since certain commercial thromboplastins used to measure the prothrombin time are more sensitive to LAC than others and can cause artifactual prolongation of the INR, and thus subtherapeutic VKA dose,[51] lupus insensitive reagents should ideally be used. The LAC interference can also be seen with the use of some point-of-care INR devices; caution is therefore recommended.[30,51]

Table 2: Randomised controlled trials evaluating the antithrombotic treatment in patients with antiphospholipid antibodies.

Study	Number of patients	Patients characteristics	Follow-up	Anticoagulant treatment	Arterial or venous thrombosis, n (%)	Major bleeding, n (%)
Secondary prevention						
PAPRE Crowther et al., 2003[47]	114	APS patients with aPL (LAC, aCL) and previous ATE or VTE	2.7 years (mean)	High intensity warfarin (INR target range 3.1–4.0)	6 (10.7%)	3 (5.4%)
				Moderate intensity warfarin (INR target range 2.0–3.0)	2 (3.4%)	4 (6.9%)
				HR	3.1 (95% CI: 0.6–15.0); p=0.15	1.0 (95% CI: 0.2–4.8); p=0.96
WAPS Finazzi et al., 2005[48]	109	APS patients with aPL (LAC, aCL) and previous ATE or VTE	3.6 years (median)	High-intensity warfarin (INR target range 3.0–4.5)	6 (11.1%)	2 (3.7%)
				Standard antithrombotic therapy (warfarin with INR target range 2.0–3.0 or aspirin 100 mg daily)	3 (5.5%)	3 (5.5%)
				HR	1.97 (95% CI: 0.49–7.89); p=0.3383	0.66 (95% CI: 0.11–3.96); p=0.6518
Okuma et al., 2010[57]	20	APS patients with aPL (LAC, aCL) and ischaemic stroke	3.9 years (mean)	Single antiplatelet therapy (aspirin 100 mg daily)	Only stroke recurrence has been evaluated, and the authors said it was higher in the single antiplatelet group (log-rank test; p=0.026), but number of subjects not reported	1 (9.1%)
				Antiplatelet and anticoagulation therapy (INR target range 2.0–3.0)		0
RAPS Cohen et al., 2016[53]	116	APS patients with aPL (LAC, aCL, aβ2-GPI) and previous VTE, on warfarin treatment	0.5 years	Rivaroxaban 20 mg once daily (or 15 mg daily as appropriate)	0	0
				Standard-intensity warfarin (INR target range 2.0–3.0)	0	0
				HR	N/A	N/A

Table 2 continued.

Study	Number of patients	Patients characteristics	Follow-up	Anticoagulant treatment	Arterial or venous thrombosis, n (%)	Major bleeding, n (%)
TRAPS Pengo et al., 2018[54]	120	APS patients with triple positivity (LAC, aCL and aβ2-GPI) and previous ATE or VTE	1.6 years (mean)	Rivaroxaban 20 mg once daily (or 15 mg daily as appropriate)	7 (12.0%)	4 (7.0%)
				Standard-intensity warfarin (INR target range 2.0–3.0)	0	2 (3.0%)
				HR	N/A	2.5 (95% CI: 0.5–13.6); p=0.3
Primary prevention						
APLASA Erkan et al., 2007[60]	98	Asymptomatic patients with aPL (LAC, aCL)	2.3 years (mean)	Aspirin 81 mg daily	3 (6.3%) [2.75 per 100 patient-years]	0
				Placebo	0 [0 per 100 patient-years]	0
				HR	1.04 (95% CI: 0.69–1.56); p=0.83	N/A
ALIWAPAS Cuadrado et al., 2014[61]	166	Patients with aPL (LAC, aCL) and SLE and/or obstetric morbidity	3.1 years (median)	Aspirin and low-intensity warfarin (INR target range 1.3–1.7)	4 (4.8%) [1.8 per 100 patient-years]	0
				Aspirin 75–125 mg daily	4 (4.9%) [1.7 per 100 patient-years]	0
				HR	1.07 (95% CI: 0.27–4.29); p=0.92	N/A

aβ2-GPI: anti-β2 glycoprotein-I; aCL: anticardiolipin antibodies; aPL: antiphospholipid antibodies; APLASA: antiphospholipid antibody acetylsalicylic acid; APS: antiphosphoplipid syndrome; ATE: arterial thrombotic events; CI: confidence interval; HR: hazard ratio; INR: international normalised ratio; LAC: lupus anticoagulant; N/A: not applicable; PAPRE: patients with antiphospholipid antibodies prevent recurrent events; RAPS: rivaroxaban in antiphospholipid syndrome; SLE: systemic lupus erythematous; VTE: venous thromboembolism; WAPS: warfarin in the antiphospholipid syndrome.

Recurrent thrombosis during VKA treatment at therapeutic INR (warfarin failure) is a known complication of APS[52] and can lead to different management strategies, such as increasing the INR target range, shifting to LMWH, or adding low-dose aspirin.[50]

There are two published RCT evaluating the use of rivaroxaban compared to warfarin in APS patients (Table 2). The RAPS trial used a surrogate endpoint (the change in the endogenous thrombin potential from randomisation to Day 42) and showed no clinical events in either groups during the 6-month follow-up.[53] The TRAPS trial enrolled only APS patients with triple positivity and was prematurely interrupted due to an excess of arterial thrombotic complications in the rivaroxaban arm.[54] A RCT evaluating apixaban is ongoing.[55]

The treatment of APS patients presenting with ATE is less defined, since few patients with ATE

were enrolled in the RCT evaluating the VKA.[47,48] Possible therapeutic options include aspirin alone (e.g., in elderly patients presenting with stroke), VKA at standard INR target range or high-intensity warfarin (INR target range 3–4),[50] and the combination of VKA and low-dose aspirin (e.g., after failure of single antithrombotic therapy).[56,57] It is also important to act on risk factors for ATE, such as hypertension, hyperlipidaemia, obesity, and smoking.

In women with obstetrical APS, the combination of prophylactic-dose LMWH (or prophylactic/intermediate-dose UFH) and low-dose aspirin is usually prescribed to prevent pregnancy complications,[58] based on the evidence that this association may halve the risk of pregnancy loss.[59] Heparin should be continued for 6 weeks after birth, because of the high thrombotic risk during the puerperium.[50] Close monitoring of the fetus and the mother during pregnancy is also suggested, to identify placental insufficiency or fetal distress.[5]

The need for primary thromboprophylaxis in asymptomatic aPL carriers without any previous thrombotic event is debated. Primary prevention RCT (Table 2) showed scarce benefit of low-dose aspirin or aspirin and warfarin, considering the low annual incidence rate of thrombosis in this population.[60,61] The guidelines of the British Committee for Standards in Haematology discourage the use of primary thromboprophylaxis in individuals with incidentally discovered aPL.[30] Vice versa, the consensus document elaborated by an international Task Force at the 13th International Congress on aPL recommends low-dose aspirin for SLE patients with aPL and suggests the same thromboprophylaxis for non-SLE individuals with high-risk aPL profile (LAC, triple positivity, or aCL at medium-high titre).[62] It has been estimated that the annual risk of a first thrombotic events is <1% in subjects with aPL without any other risk factors, compared to 5% in patients with a high-risk aPL profile associated with systemic autoimmune diseases.[50]

Other Treatments

Additional treatment strategies are used to address the clinical manifestations of APS. Hydroxychloroquine has anti-inflammatory and anti-thrombotic properties and is recommended by recent consensus guidelines as primary thromboprophylaxis in patients with aPL, SLE, and no contraindications, where it was shown not only to protect against thrombosis, but also to increase survival.[62] Furthermore, hydroxychloroquine may have a role as adjuvant therapy in APS with recurrent thrombosis despite adequate anticoagulant treatment.[50,62]

Statins have pleiotropic effects, including anti-inflammatory and anti-thrombotic properties. Two recent studies showed that fluvastatin can reduce pro-inflammatory and pro-thrombotic markers in aPL patients, while pravastatin can improve pregnancy outcomes in women with obstetrical APS.[6]

Rituximab is a monoclonal antibody against CD20 located mainly on B-lymphocytes. There is recent evidence that rituximab may be effective in controlling some non-criteria manifestations of APS (such as thrombocytopenia, haemolytic anaemia, and skin ulcers) and can also be an option for refractory CAPS.[50,63] Another monoclonal antibody, eculizumab, a C5 complement inhibitor, can be effective in refractory CAPS, blocking the widespread complement activation, and preventing recurrent APS post-kidney transplantation in patients with aPL-related nephropathy.[50]

Catastrophic Antiphospholipid Syndrome

Treatment of CAPS should aim at the control of any precipitating factor, as well as the prevention and treatment of thrombosis. In a proposed treatment algorithm for CAPS, prompt use of anticoagulation (usually intravenous UFH) and high dose corticosteroids represented the first-line option, with the addition of intravenous immunoglobulin and/or plasma exchange (to remove pathogenic aPL and the excess of cytokines) in life-threatening conditions.[23] In the CAPS registry, the combination of anticoagulant, steroids, and plasma exchange obtained a recovery rate of 77.8%.[64] Rituximab and eculizumab are second-line options in refractory CAPS, although they are only supported by a few case-reports.[50]

CONCLUSION

APS is a rare autoimmune disease characterised by significant morbidity and mortality. The

diagnosis of APS needs the simultaneous presence of clinical and laboratory criteria. Laboratory tests should be performed according to international guidelines, which are periodically updated. The treatment of APS patients presenting with VTE, ATE, or obstetrical APS may differ, but anticoagulation usually plays a substantial role. New emerging treatments may provide additional strategies to address the clinical manifestations of APS in the future.

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Secukinumab in the Management of Psoriatic Arthritis: Current Perspectives

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Abstract

Psoriatic arthritis (PsA) is a seronegative, inflammatory arthritis associated with cutaneous psoriasis. This disease is associated with significant morbidity, thus requiring early treatment initiation and reduction of disease activity. Anti-cytokine therapies are increasingly being used for the treatment of PsA. In addition to the anti-TNF agents, monoclonal antibodies targeting IL-17 have been approved for the treatment of PsA. Secukinumab is a monoclonal antibody against IL-17 and is currently approved for the management of PsA. In this literature-based review, the current status of secukinumab for the management of PsA is discussed.

INTRODUCTION

Psoriatic arthritis (PsA) belongs to the group of diseases known as spondyloarthritis (SpA). The impact of PsA is not limited to just skin and joints, but also includes various extra-articular manifestations and co-morbidities. Asymmetric oligo-arthritis associated with skin psoriasis is the classical presentation of PsA. At present, the Classification Criteria for Psoriatic Arthritis (CASPAR) is used for the diagnosis of PsA.[1] With expanding insight into PsA pathogenesis, the roles of various cytokines are becoming more evident, and currently cytokine-targeted therapies are important research topics in the management of PsA. The role of IL-17 in the pathogenesis of PsA has been proven through various studies, and therapies involving monoclonal antibody-targeting of IL-17 are gaining importance in the management of PsA. Secukinumab is a fully human monoclonal antibody that binds to IL-17 and prevents its interaction with the IL-17 receptor. Various clinical trials have shown the beneficial effects of secukinumab in the management of PsA. In this review, the efficacy and safety of secukinumab are discussed in light of currently available research data.

SEARCH METHODS

Clinical trials and reviews were searched for using the Pubmed database. The following search terms were used: "Interleukin-17", or "Secukinumab", and/or "Psoriatic arthritis", all of which were selected without time frame or publication date specification. Search items also included efficacy, safety, and radiographic progression (e.g., "Secukinumab efficacy", "Secukinumab safety").

IL-17 IN THE PATHOGENESIS OF PSORIATIC ARTHRITIS

The IL-17 group of cytokines consists of six members: IL-17A–F.[2] This recently discovered group of cytokines has led to a paradigm shift in the understanding of SpA pathogenesis. Th-17 cells are important sources of IL-17, and TGF-β1, IL-1β, IL-6, and IL-21 are the polarising cytokines needed by the naïve T cells to transform into Th-17 cells.[3,4] Survival of the Th-17 cells is dependent on IL-23.[5] In addition to the IL-17 family, various other cytokines are produced by Th-17 cells. Additionally, production of IL-17 is not merely restricted to the Th-17 cells, but also includes γδ T cells, mast cells, neutrophils, ILC 3 cells, and Tc-17 cells.[6] It has been shown that synovial fluid from PsA patients contains a large number of IL-17-producing CD4+ T cells compared to patients with osteoarthritis, where both IL-17 and its associated receptor are abundantly expressed.[7] An increased number of IL-17-producing CD8+ T cells are also seen in the synovial fluid of PsA patients compared to healthy controls.[8] All these observations point towards a strong pathogenic role of IL-17 in PsA and rationale for targeting this cytokine for the management of this disease.

CLINICAL TRIALS WITH ANTI-IL-17 MONOCLONAL ANTIBODY IN PSORIATIC ARTHRITIS: SECUKINUMAB

Secukinumab is a fully human monoclonal antibody of the IgG1 subclass which binds to and neutralises IL-17, thereby preventing its binding with receptors. IL-17 acts as a pro-inflammatory cytokine. It induces the production of IL-1 and TNF-α. IL-17 promotes osteoclastogenesis by upregulating osteoblast receptor activation by NF-κB ligand. As a result of IL-17 neutralisation by secukinumab, the pro-inflammatory effects of this cytokine are blocked. Secukinumab has a proven efficacy and safety profile for the treatment of PsA.

EFFICACY IN PSORIATIC ARTHRITIS DISEASE ACTIVITY, SKIN SCORE, FUNCTIONAL STATUS

In a Phase II, proof of concept trial by McInnes et al.,[9] secukinumab did not meet the primary endpoint for the American College of Rheumatology 20 (ACR20) response at Week 6 compared to placebo; however, it showed improvement of acute phase reactant levels and quality of life in PsA patients.

The FUTURE 1 study was the first Phase III randomised control trial that showed the efficacy of secukinumab in PsA. In this study, 606 PsA patients were recruited and secukinumab was administered as an intravenous loading dose (LD) of 10 mg/kg at Weeks 0, 2, and 4, followed by subcutaneous injections of either 150 mg or 75 mg every 4 weeks. At Week 24, ACR20 response rates were significantly higher in the secukinumab group compared to the placebo (150 mg [50.0%] and 75 mg [50.5%], placebo [17.3%]; p<0.001 for both comparisons). ACR50 response at Week 24 was also observed in a larger proportion of patients in the secukinumab group compared to the placebo group (150 mg [34.7%] and 75 mg [30.7%], placebo [7.4%]; p<0.001). Significant improvements in Psoriasis Area Severity Index 75 and 90 (PASI 75 and 90) were observed, and sustained efficacy was noted up to 52 weeks. Importantly, 17–19% of secukinumab-treated patients (75 mg and 150 mg groups) were inadequate responders to at least one TNF-inhibitor. Improvement of ACR20 response was observed in these patients also, suggesting the use of IL-17 blockade as an alternative treatment option in these patients.[10] In the 3-year extension phase of the FUTURE 1 cohort, persistent efficacy in all endpoints, including ACR20 response, improvement of quality of life, and physical function, were documented in the secukinumab group. ACR20 response at Week 156 was observed in 76.8% and 65.2% of patients from the 150 mg and 75 mg groups, respectively. ACR50/70 responses for these two groups were 54.9/32.9% and 39.0/26.0%, respectively. The ACR20 response was proportionally higher in the anti-TNF naïve patients (81.0% and 67.3% in 150 mg and 75 mg groups, respectively) compared to the previous anti-TNF-experienced patients (61.5% and 55.6% in 150 mg and 75 mg groups, respectively).[11] The response rate of secukinumab observed in the FUTURE 1 trial has been summarised in Table 1.

FUTURE 2 was a multicentre, placebo-controlled, Phase III trial that included 397 patients with active PsA. In this trial, no intravenous LD was used; instead, subcutaneous secukinumab of 75, 150, or 300 mg or placebo was given at Weeks 0, 1, 2, 3, and 4, followed by the same dose every 4 weeks.

Table 1: Efficacy of secukinumab on the basis of American College of Rheumatology (ACR) responses in the FUTURE 1 and 2 studies.

	ACR Responses		
	ACR20	ACR50	ACR70
FUTURE 1 At Week 24	10 mg/kg IV then 150 mg SC: 50.0% (p<0.001) 10 mg/kg IV then 75 mg SC: 50.5%% (p<0.001) Placebo: 17.3%	10 mg/kg IV then 150 mg SC: 34.7% (p<0.001) 10 mg/kg IV then 75 mg SC: 30.7% (p<0.001) Placebo: 7.4%	10 mg/kg IV then 150 mg SC: 18.8% (p<0.001) 10 mg/kg IV then 75 mg SC: 16.8% (p<0.001) Placebo: 2.0%
At Week 52	10 mg/kg IV then 150 mg SC: 69.5% (observed data) and 59.9% (missing data imputed as no response). 10 mg/kg IV then 75 mg SC: 66.9% (observed data) and 56.9% (missing data imputed as no response).	10 mg/kg IV then 150 mg SC: 50.0% (observed data) and 43.1% (missing data imputed as no response). 10 mg/kg IV then 75 mg SC: 38.4% (observed data) and 32.7% (missing data imputed as no response).	10 mg/kg IV then 150 mg SC: 28.2% (observed data) and 24.3% (missing data imputed as no response). 10 mg/kg IV then 75 mg SC: 25.6% (observed data) and 21.8% (missing data imputed as no response).
FUTURE 1, 3-year extension study At Week 156	150 mg: 76.8% 75 mg: 65.2%	150 mg: 54.9% 75 mg: 39.0%	150 mg: 32.9% 75 mg: 26.0%
FUTURE 2. At Week 24	300 mg: 54% (p<0.0001) 150 mg: 51% (p<0.0001) 75 mg: 29% (p=0.3990) Placebo: 15%	300 mg: 35% (p=0.0040) 150 mg: 35%(p=0.0555) 75 mg: 18% (p=0.9195) Placebo: 7%	300 mg: 20% (p=0.0040) 150 mg: 21% (p=0.0555) 75 mg: 6% (p=0.9195) Placebo: 1%
At Week 52	300 mg: 73% (actual data) and 64% (missing data imputed as non-response). 150 mg: 73% (actual data) and 64% (missing data imputed as non-response). 75 mg: 67% (actual data) and 51% (missing data imputed as non-response).	300 mg: 50% (actual data) and 44% (missing data imputed as non-response). 150 mg: 44% (actual data) and 39% (missing data imputed as non-response). 75 mg: 40% (actual data) and 30% (missing data imputed as non-response).	300 mg: 27% (actual data) and 24% (missing data imputed as non-response). 150 mg: 23% (actual data) and 20% (missing data imputed as non-response). 75 mg: 21% (actual data) and 16% (missing data imputed as non-response).
FUTURE 2, 2-year extension At Week 104	300 mg: 69.4% (missing data imputed as non-response) and 73.8% (observed data). 150 mg: 64.4% (missing data imputed as non-response) and 72.7% (observed data). 75 mg: 50.3% (missing data imputed as non-response) and 62.7% (observed data).	300 mg: 50.6% (missing data imputed as non-response) and 56.0% (observed data). 150 mg: 36.0% (missing data imputed as non-response) and 42.9% (observed data). 75 mg: 28.2% (missing data imputed as non-response) and 37.3% (observed data).	300 mg: 33.1% (missing data imputed as non-response) and 38.1% (observed data). 150 mg: 23.1% (missing data imputed as non-response) and 28.6% (observed data). 75 mg: 14.9% (missing data imputed as non-response) and 20.9% (observed data).

IV: intravenous; SC: subcutaneous.

Patients of the placebo group were re-randomised based on their response status at Week 16. Non-responders received secukinumab (150 mg or 300 mg every 4 weeks) from Week 16, and responders from Week 24. From an efficacy viewpoint, both 300 mg and 150 mg secukinumab dosages elicited significantly more ACR20 responses compared to placebo ($p<0.0001$). ACR20 responses at Week 24 were seen in 54%, 51%, and 29% of patients from the 300mg, 150 mg, and 75 mg dosage groups, respectively, compared to 15% of patients from the placebo group. Response rates for the 75 mg secukinumab group were not statistically different from the placebo group ($p=0.399$), and ACR20 response was sustained through Week 52. ACR50 response was also higher in both secukinumab 300 mg (35%) and 150 mg (35%) groups, compared to the 75 mg (18%) and placebo group (7%). The proportions of patients with inadequate response to at least one TNF inhibitor were 16%, 26%, and 21% in the 300 mg, 150 mg, and 75 mg groups, respectively. Higher ACR response rates were observed in both the anti-TNF naïve and anti-TNF inadequate responders, but response magnitude was higher in the anti-TNF naïve populations. In exploratory analyses, ACR70 response was achieved in 20% and 21% of patients from the 300 mg and 150 mg groups, respectively. These values were higher than the 75 mg (6%) and placebo (1%) groups. Other secondary endpoints, including PASI 75 and PASI 90 response rates and mean changes of DAS28 C-reactive protein from baseline, were significantly higher in the secukinumab 300 mg and 150 mg groups.[12] Results from the 2-year extension phase of the FUTURE 2 trial showed persistent improvement of ACR20 response across all three dosage schedules (69.4% in 300 mg, 64.4% in 150 mg, and 50.3% in 75 mg groups). It is important to note that there was sustained increase in the proportion of patients with an ACR20 response over time, not only in the 300 mg and 150 mg groups, but also in the 75 mg group. Sustained clinical response was noted in both anti-TNF naïve and anti-TNF inadequate responders; however, the proportion of patients with ACR20, 50, and 70 rates were higher in the anti-TNF naïve patients. Improvement in functional status and quality of life was also documented.[13] Response rates of secukinumab observed in the FUTURE 2 trial has been summarised in Table 1.

The FUTURE 3 trial was designed to find the efficacy and safety of self-administered subcutaneous secukinumab by autoinjector. This study is still ongoing, and the 52-week data has showed significant efficacy of secukinumab as assessed by ACR20 response compared to placebo. More importantly, >99% of patients were able to self-administer the drug at Week 1 successfully. Absence of pain or reaction was reported by >90% of the users, and almost 88% of patients were either satisfied or very satisfied with the use of autoinjector and opined in favour of its user-friendliness.[14]

The FUTURE 4 study is intended to find out the safety and efficacy of subcutaneous secukinumab 150 mg with or without a LD compared to the placebo. This study is still ongoing, with an abstract having been published at the Pan-American League of Association for Rheumatology (PANLAR) congress in Buenos Aries, Argentina, in 2018. In concordance with the previous trials, it showed significantly higher ACR20 response rates in the secukinumab groups at Week 16 (41.2% in 150 mg, LD; 39.8% in 150 mg, no LD; and 18.4% in placebo; $p<0.001$ for both secukinumab groups versus placebo). These improvements were sustained up to 52 weeks. Clinical responses were observed in both anti-TNF naïve and inadequate responders; however, the former group showed better responses. PsA patients who received LD showed earlier and better responses than those who did not, and this was mostly observed in the TNF inadequate responders. To summarise, LD of secukinumab may be more effective in PsA patients who have previously shown inadequate response to anti-TNF agents.[15]

FUTURE 5 is another ongoing trial, aimed at evaluating secukinumab efficacy in reducing symptoms and radiographic progression among PsA patients. In this large study with 996 patients with active PsA, the following three dosage regimens of secukinumab have been used: 300 mg or 150 mg with LD, and 150 mg without LD. ACR20 response at Week 16 were achieved in significantly more proportions of patients in the secukinumab groups compared to the placebo (300 mg with LD [62.6%], 150 mg with LD [55.5%], 150 mg without LD [59.5%], and placebo [27.4%] [$p<0.0001$ for all]).

This is, however, short-term data, and we must wait for further results to be released.[16]

Table 2: Efficacy of secukinumab in the resolution of dactylitis.

Study Name	Resolution of dactylitis	
	Secukinumab	Placebo
Mease et al.,[10] 2015. FUTURE 1		
At 24 weeks	Pooled data: 52.4%	15.5%
At Week 52	10 mg/kg IV then 150 mg SC: 82.0% 10 mg/kg IV then 75 mg SC: 84.4%	
At Week 104	10 mg/kg IV then 150 mg SC: 86.5% 10 mg/kg IV then 75 mg SC: 88.6%	——
At Week 156	10 mg/kg IV then 150 mg SC: 88.1% 10 mg/kg IV then 75 mg SC: 86.8%	
McInnes et al.,[12] 2015. FUTURE 2		
At Week 24	Pooled data: 47%	15.0%
At Week 104 (considering missing values)	300 mg: 79.9% 150 mg: 78% 75 mg: 88.6%	
Nash et al.,[14] 2018. FUTURE 3		
At Week 24	300 mg: 47.8% 150 mg: 38.9%	13.9%
At Week 52	300 mg: 60.9% 150 mg: 52.8%	

IV: intravenous; SC: subcutaneous.

ROLE IN MANAGEMENT OF DACTYLITIS

Dactylitis is defined as swelling of an entire digit that is not merely restricted to joints and is frequently seen in patients with SpA. In a recent study with 1,282 PsA patients, dactylitis was identified in 59.2% of patients.[17] An earlier Canadian study with 537 PsA patients showed that dactylitis was found in 48.0% of patients.[18] Indeed, dactylitis may be present in 29.0–33.5% of PsA patients at first presentation.[19] Flexor tendon tenosynovitis and synovitis of joints are the most commonly described pathologies in dactylitis. Soft tissue thickening and extensor tendonitis may also be present. Some studies have demonstrated a link between dactylitis and digital polyenthesitis.[20,21]

Data from the FUTURE trials showed the beneficial effect of secukinumab in the resolution of dactylitis. In the FUTURE 1 trial, 51.5% of PsA patients of both 150 mg and 75 mg groups had dactylitis. After 24 weeks of treatment, 52.4% of patients had resolution of dactylitis (combined data of both groups), compared to 15.5% in the placebo group.[10] This effect was sustained and increased with continuation of secukinumab, and resolution of the condition at Week 156 was seen in 88.1% and 86.8% of patients of 150 mg and 75 mg dosages, respectively.[11]

The proportion of patients with dactylitis was somewhat less in the FUTURE 2 trial (46%, 32%, and 33% in dosage groups 300 mg, 150 mg, and 75 mg, respectively). Analysis of pooled data regarding resolution of dactylitis across all secukinumab groups did not show any significant difference from placebo (p=0.9195).[12]

The proportion of patients with dactylitis resolution at Week 104 was much higher than

Table 3: Efficacy of secukinumab in the resolution of enthesitis.

Study Name	Resolution of enthesitis	
	Secukinumab	Placebo
Mease et al.[10] FUTURE 1 At 24 weeks At Week 52 At Week 104 At Week 156	 Pooled data: 47.5% 10 mg/kg IV then 150 mg SC: 74.8% 10 mg/kg IV then 75 mg SC: 75.6% 10 mg/kg IV then 150 mg SC: 74.5% 10 mg/kg IV then 75 mg SC: 80.3% 10 mg/kg IV then 150 mg SC: 76.7% 10 mg/kg IV then 75 mg SC: 74.8%	 12.8%
McInnes et al.,[12] 2015. FUTURE 2 At Week 24 At Week 104 (considering missing values)	 Pooled data: 40.0% 300 mg: 71.5% 150 mg: 61.8% 75 mg: 68.4%	 22.0%
Nash et al.,[14] 2018. FUTURE 3 At Week 24 At Week 52	 300 mg: 39.8% 150 mg: 36.8% 300 mg: 53.4% 150 mg: 46.3%	 15.3%

IV: intravenous; SC: subcutaneous.

that observed at Week 24. Analysis based on the observed data showed that 88.5% (300 mg group), 92.2% (150 mg group) and 95.6% (75 mg group) of patients were free from dactylitis. These proportions were slightly lower when the analysis was done based on missing values as non-responders (79.9%, 78.0%, and 88.6% for 300 mg, 150 mg, and 75 mg, respectively).[13]

The Week 52 results from the FUTURE 3 trial showed dactylitis resolution rates of 60.9% and 52.8% for the 300 mg and 150 mg groups, respectively.[14] Data from all these studies have clearly documented the efficacy of secukinumab in the management of dactylitis in patients with PsA. It is also obvious that improvement of dactylitis occurs with longer treatment duration. The efficacy of secukinumab in the resolution of dactylitis is presented in Table 2.

ROLE IN MANAGEMENT OF ENTHESITIS

Enthesitis is defined as inflammation at the sites of tendon and ligament insertion into the bone. In PsA, enthesitis may be a presenting feature or may appear later in the disease course. It has an estimated prevalence of 35.0%, and an annual incidence of 0.9%. Common sites of enthesitis are at the Achilles tendon insertion, plantar fascia, or the lateral epicondyles, but other sites may also be involved.[22] The efficacy of secukinumab in the resolution of enthesitis has been documented in previous studies. After 52 weeks of treatment with secukinumab, enthesitis resolution proportion ranges from 46.3–80.3% in different studies.[11,13,14] Enthesitis resolution rate increases with longer treatment duration. The efficacy of secukinumab in the resolution of enthesitis has been presented in Table 3.

EFFECT ON RADIOGRAPHIC PROGRESSION

Retardation of radiographic progression is another important goal in the management of PsA. Both erosion and osteoproliferation are characteristic features of bony changes in PsA. It has been estimated that 12–47% of PsA patients develop bony erosions within 2 years of disease onset.[19] The combination of systemic bone loss, along with new bone formation at entheseal and periosteal sites in the SpA group, is possibly mediated by IL-23 and IL-17.[23-25] IL-17 promotes osteoclastogenesis thorough a signalling cascade that leads to NFκB ligand expression on osteoblasts, causing their subsequent differentiation into osteoclasts.[26,27] IL-17 also has a direct effect on osteoclast differentiation.[28] On the contrary, the effect of IL-17 on osteoblasts is yet to be clearly elucidated. Evidence from various studies is both contradictory and supportive regarding the inhibitory effect of IL-17 on osteoblasts.[29,30] A recent review concluded that the effect of IL-17 on the osteoblast depends upon multiple factors, including type of cell exposed to IL-17, the differentiation stage of that cell, and the timing and duration of IL-17 exposure.[31]

The effect of secukinumab on radiographic progression in PsA is quite encouraging. Data from the FUTURE 1 trial showed that patients who received secukinumab had significantly less radiographic progression than placebo group at Week 24, as assessed by mean change of van der Heijde-modified total Sharp score (mTSS) from baseline (0.13 for 150 mg group, 0.02 for 75 mg group, 0.08 for secukinumab pooled doses, and 0.57 for placebo group). At Week 52, mean changes of mTSS from baseline were 0.37, 0.22, and 0.30 for the 150 mg, 75 mg, and pooled dose groups, respectively. Three-year data showed 78.1% (150 mg) and 74.8% (75 mg) patients were radiographic non progressors (non-progression was defined as patients who had a change from baseline of ≤0.5 in mTSS during observation period).[11] Sub group analysis did not show any significant difference in the proportion of patients with radiographic nonprogression between anti-TNF naïve and anti-TNF experienced patients. In the secukinumab 150 mg arm, 78.0% (anti-TNF naïve) and 78.6% (anti-TNF experienced) patients were non progressors, whereas in the 75 mg arm these values were 77.7% and 65.5% respectively.[11]

The recently published primary result of the ongoing FUTURE 5 trial is also in favour of the beneficial effect of secukinumab in radiographic progression in PsA. At Week 24, the mean changes of mTSS from baseline were significantly lower in all secukinumab arms compared to the placebo arm. The proportions of radiographic non-progressors at 24 weeks were 88.0% (300 mg with LD), 79.8% (150 mg with LD), 83.8% (150 mg without LD), and 73.6% (placebo).[16] It is notable that significant proportions of patients in the placebo group were also radiographic non-progressors. However, these data were based on a 24-week observation period and radiographic progression was assessed by X-ray. Consequently, significant changes in radiographic score may not be observed within this short time frame. Long-term data of this study may provide additional information regarding this issue.

In previous studies, radiographic progression was assessed by X-ray. It may take a longer time to appreciate significant changes by this imaging technique. MRI and CT can detect bony changes earlier than X-ray. In an open label study by Kampylafka et al.,[32] with 20 active PsA patients, changes in the hand joints after 24 weeks of secukinumab treatment were assessed by MRI, power doppler ultrasound, and high-resolution peripheral quantitative CT. They searched for changes in the status of synovitis, periarticular inflammation, bone erosion, enthesiophyte formation, and bone structure. There was no progression in bone erosions or enthesiophytes as detected by MRI and high-resolution peripheral quantitative CT. Secukinumab treatment resulted in cessation of progression of both catabolic and anabolic bone changes in the peripheral joints of PsA patients.[32] Data available so far from these studies is clearly indicative of protective effects of secukinumab in the radiographic progression of PsA. Sensitive imaging modalities can detect this effect earlier than through conventional radiography.

SAFETY DATA

For the widespread use of any biologic agent, safety issues are a major concern. Adverse event rates from the FUTURE 1 trial during the 16-week placebo controlled period did not show any significant difference between secukinumab and placebo groups (64.9% in 150 mg, 60.4% in 75 mg,

and 58.4% of patients in the placebo group).[10] Most of the adverse events were of mild-to-moderate degree. During the 104-week extension periods of the FUTURE 1 and 2 trials, nasopharyngitis was a common adverse event noted in the secukinumab group (among 13.4% and 13.6% patients in FUTURE 1 and 2 trials, respectively), followed by upper respiratory tract infections (among 12.6% of patients in both FUTURE 1 and 2 trials). Diarrhoea and headache were also seen, but less frequently. Oral candidiasis was reported in four patients each in the 150 mg and 75 mg groups (approximately in 2% of patients). No treatment withdrawal was required for *candida* infection. New tuberculosis or its reactivation was not reported. Neutropaenia was also reported in both FUTURE 1 and 2 trials, but rates of malignancy or inflammatory bowel disease were quite low. In the FUTURE 1 trial, exposure-adjusted rates of serious events among secukinumab 150 mg and 75 mg arms were 11.5 and 7.4 per 100 patient-years, respectively. During the safety period, four patients in the secukinumab 75 mg group had a stroke (exposure-adjusted rate: 0.6/100 patient-years). Two patients from both 150 mg and 75 mg groups experienced myocardial infarction (rate: 0.3/100 patient-years). Drug discontinuation rates were low across all these trials. Drug discontinuation rate in the 156-week extension period of the FUTURE 1 trial were 6.21% and 3.40% in secukinumab 150 mg and 75 mg groups, respectively (data from patients in extension full analysis set).[11] Two year data from FUTURE 2 trial showed that 86% and 76% of patients in the 300 mg and 150 mg groups, respectively, completed the 104-week trial period.[13]

ADDITIONAL THERAPIES

In addition to secukinumab, other molecules targeting IL-17 are also under investigation in clinical trials. Ixekizumab is a humanised, monoclonal antibody targeting IL-17. One recent trial evaluated the efficacy of this biological agent in the management of PsA. Initial reports of a Phase III trial with ixekizumab in biologic-naïve PsA patients (SPIRIT-P1) showed the efficacy of this agent in reducing disease activity and improving physical function.[33] Fifty-two week data of the SPIRIT-P1 trial also showed sustained efficacy and reasonable safety profile of this drug in PsA.[34] Bimekizumab neutralises both IL-17 and IL-17F. One recent proof of concept trial showed its efficacy in PsA.[35] Brodalumab is a fully human, recombinant monoclonal antibody of IgG2 subclass which binds to the high affinity receptor IL-17RA. It is already approved for the management of severe plaque psoriasis, and some previous studies have shown its efficacy in the treatment of PsA. However, suicidal tendency may be a major symptom concerning the use of Brodalumab.

CURRENT RECOMMENDATIONS FOR USE OF SECUKINUMAB AND OTHER BIOLOGICS IN PSORIATIC ARTHRITIS

Secukinumab is being approved by the European Medicines Agency (EMA) for the treatment of adult patients with active PsA. As per the European League Against Rheumatism (EULAR) guidelines, IL-17-targeted therapy can be used in PsA patients with peripheral arthritis not/inadequately responding to at least one conventional synthetic disease-modifying antirheumatic drug and in whom anti-TNF therapy is not suitable for use. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommends for the use of any biologics (anti-TNF, anti-IL-12/23) in PsA patients with peripheral arthritis, even at an earlier stage if poor prognostic factors are present. IL-17-targeted therapy has been conditionally recommended, as Phase III data regarding secukinumab were not fully published at the time of publication of this guideline. For nail psoriasis, biologics (anti-TNF, anti-IL-12/23, or anti IL-17) are the preferred initial therapy. For the management of skin psoriasis, GRAPPA recommends biologics if conventional treatment fails; however, in severe disease, biologics can be used as the initial therapy. For dactylitis, biologics (anti-TNF, anti-IL-12/23) are recommended if conventional therapy fails or even as initial therapy. Anti-IL-17 is again conditionally recommended. For enthesitis, biologics or non-steroidal anti-inflammatory drugs can be used in non-responders to physiotherapy.

CONCLUSIONS

Currently available data are clearly indicative of the significant efficacy of anti-IL-17 monoclonal antibodies in reducing symptoms of PsA. Three-

year data of secukinumab has also shown sustained and incremental efficacy for this agent. This drug has an acceptable safety profile and inhibitory effect on the radiographic progression in PsA. Secukinumab is approved by both the U.S. Food and Drug Administration (FDA) and EMA for the management of moderate to severe PsA. In their recent guidelines, both EULAR and the GRAPPA have included anti-IL-17 therapy for the management of PsA. On the contrary, no efficacy or safety data of secukinumab is available beyond 156 weeks. Data regarding the long-term effects on radiographic progression are also lacking beyond this duration, as well as regarding treatment duration and drug-free remission status. Results of ongoing trials may elucidate these lines of inquiry.

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A Review of Adalimumab Biosimilars for the Treatment of Immune-Mediated Rheumatic Conditions

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Abstract

Adalimumab is a recombinant fully human monoclonal antibody targeting soluble and transmembrane TNF alpha. It is approved for the treatment of immune-mediated rheumatic, gastroenterological, dermatological, and ophthalmological conditions and this therapeutic versatility has made it the top-selling drug worldwide since 2012. Not surprisingly, following the patent expiration of the originator drug, biopharmaceutical companies invested in the development of biosimilar versions of adalimumab and six have already received marketing authorisation: ABP 501, GP2017, and BI 695501 in Europe and in the USA (though the manufacturer of the latter requested authorisation withdrawal in Europe), and SB5, FKB327, and MSB11022 in Europe. This manuscript reviews published data on approved adalimumab biosimilars, including analytical and biofunctional results from preclinical assessments; pharmacokinetics after administration in healthy subjects (Phase I trials); and efficacy, safety, and immunogenicity from pivotal (Phase III) clinical trials. Data on switching from reference adalimumab to biosimilars, and predicted cost-savings from available budget impact models, will also be addressed.

INTRODUCTION

Adalimumab is a recombinant fully human monoclonal antibody (IgG1 type) targeting soluble and transmembrane TNF. AbbVie's bio-originator adalimumab, branded name Humira® (AbbVie, USA), is the top global selling drug since 2012[1] and it is approved for the treatment of immune-mediated inflammatory conditions of rheumatic, ophthalmological, dermatological, and gastroenterological nature. Adalimumab is indicated for rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis, juvenile idiopathic arthritis (polyarticular and enthesitis-related arthritis), psoriasis, hidradenitis suppurativa, adult and paediatric Crohn's disease, ulcerative colitis, and adult non-infectious uveitis. In the European Union (EU), but not in the USA, adalimumab is also indicated for non-radiographic axial spondyloarthritis, paediatric psoriasis, paediatric hidradenitis suppurativa, and paediatric non-infectious uveitis.[2]

The approaching date of patent expiration, alongside the prospect of entering a several billion-dollar market, has led biopharmaceutical manufacturers to invest in the development of biosimilar versions of adalimumab. By the time this manuscript was elaborated, six biosimilars were given positive opinions by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA): ABP 501 (Amgevita®, Solymbic®, Amjevita®, Amgen, USA), GP2017 (Hefiya®, Halimatoz®, Hyrimoz®, Sandoz, Germany), and BI 695501 (Cyltezo®, Boehringer Ingelheim, Germany) in Europe and in the USA, and SB5 (Imraldi®, Biogen, South Korea), FKB327 (Hulio®, Fujifilm Kyowa Kirin, Japan), and MSB11022 (Idacio® and Kromeya®, Fresenius Kabi, Germany) only in Europe.[3,4] Table 1 summarises adalimumab biosimilars already approved and currently being developed in highly regulated markets. In the USA, litigation between AbbVie and adalimumab biosimilar manufacturers over adalimumab's patent was resolved by a settlement that protects the patent until 2023.[5] In Europe, the patent expired in October 2018 and the first biosimilars have recently entered the market. It should be noted, however, that the manufacturer of BI 695501 requested withdrawal of marketing authorisation in Europe due to unresolved patent litigation with AbbVie in the USA.[6]

The current article performs a comprehensive review of adalimumab biosimilars approved in highly regulated markets, including available preclinical data, pharmacokinetics (PK), efficacy, safety, and immunogenicity assessments, and pharmacoeconomic considerations.

PRECLINICAL DEVELOPMENT OF ADALIMUMAB BIOSIMILARS

The stepwise, totality-of-evidence development of any biosimilar product has its mainstay in the demonstration of a high degree of similarity in analytical and biofunctional evaluations between the biosimilar candidate and reference product. After this extensive preclinical phase, an abbreviated clinical phase ensues, including the assessment of PK, efficacy, safety, and immunogenicity.[7]

Table 1: Adalimumab biosimilars already approved and currently being developed in highly regulated markets.[3,4]

Approved adalimumab biosimilars	Adalimumab biosimilars in development
ABP 501 (Amgen) - USA and Europe	M923 (Momenta Pharmaceuticals)
GP2017 (Sandoz) - USA and Europe	CHS-1420 (Coherus Biosciences)
BI 695501 (Boehringer-Ingelheim) - USA and Europe*	PF-06410293 (Pfizer)
	ONS-3010 (Oncobiologics)
SB5 (Biogen) - Europe	AVT02 (Alvotech Swiss AG)
FKB327 (Fujifilm Kyowa Kirin) - Europe	CT-P17 (Celltrion)
MSB11022 (Fresenius Kabi) - Europe	LBAL (LG Life Sciences)

*Marketing authorisation withdrawn by the manufacturer.

Adalimumab biosimilar candidates were tested against several batches of USA and Europe-sourced reference products for key quality attributes such as primary structure (molecular mass, protein sequence, and post-translational modifications), high-order (secondary and tertiary) structures, product-related and host-cell impurities, general properties, and product stability. State-of-the-art, sensitive, and orthogonal analytical methods were employed, many of them developed or adapted specifically for this purpose. Batches of biosimilar candidates were compared with reference products using pre-established similarity ranges or direct side-by-side comparisons.

After a thorough assessment of preclinical data within the marketing authorisation application, the regulatory agencies considered there was sufficient information to ensure a similar clinical performance in ABP 501, SB5, GP2017, BI 695501, FKB327, and MSB11022, despite some minor quality differences found in some of these candidates, which were duly justified and were not expected to impact PK, efficacy, or safety.[8-13] For instance, SB5 had a slightly higher amount of free sulfhydryl groups, as well as charged N-glycans and acidic variants compared to reference adalimumab.[9] FKB327, on the other hand, showed differences in the glycosylation profile, with higher mannose content.[12] This difference led inclusively to further *in vitro* bioassay testing and PK data statistical reanalysis, before similarity was confirmed.[12]

Due to the pleiotropic nature of TNF, all known adalimumab mechanisms of action with potential clinical relevance must be compared *in vitro*. Furthermore, biofunctional testing also demonstrates that differences in quality attributes, should they exist (for instance, post-translational modifications), do not impact *in vitro* biological activity. Biofunctional data provided by ABP 501, SB5, GP2017, BI 695501, FKB327, and MSB11022 manufacturers showed a high degree of similarity in both Fab and Fc-mediated functions, including, but not limited to, binding and neutralisation of soluble and transmembrane TNF; binding to FcRn, FcγRIa, FcγRIIa, and FcγRIIIa receptors; and antibody-dependent and complement-dependent cytotoxicity.[9,11-15]

Although not mandatory, most of these biosimilar manufacturers provided PK and toxicology assessments in animal models in the data package presented to the regulatory agencies, once again demonstrating a high degree of similarity to reference products.

CLINICAL PERFORMANCE OF ADALIMUMAB BIOSIMILARS

All biosimilar candidates demonstrated PK equivalence with EU and USA-sourced reference adalimumab in Phase I trials performed in healthy subjects, with the confidence intervals of the primary endpoints (area under the curve [AUC] and maximum drug concentration [Cmax]) falling within the prespecified range of 0.80–1.25 (Table 2).[16-21] In accordance with regulatory requirements, Phase III trials were performed using a randomised, double-blind, parallel-group design. RA was chosen as the disease population in all but MSB11022, which was tested in patients with plaque-type psoriasis; ABP 501 and GP2017 also have available studies in this condition (Table 3). All biosimilar candidates confirmed similar efficacy, safety, and immunogenicity to reference adalimumab.[18,22-28]

Efficacy

In Phase III trials, biosimilar candidates must demonstrate equivalence to their reference drug, in contrast with pivotal trials of bio-originators in which superiority over placebo is the endpoint. From a statistical point of view, this means that the confidence intervals of the primary efficacy endpoint(s) must be contained within prespecified equivalence margins that are calculated for each biosimilar drug based on historical data from the reference product and by comparison with prior study designs.[29]

Primary efficacy endpoints were met in all Phase III trials in RA, namely similar American College of Rheumatology 20% (ACR20) improvement criteria responses at Week 24 between reference adalimumab and ABP 501,[22] SB5,[24] BI 695501,[26] and FKB327,[27] and similar mean change in disease activity score-28 including high-sensitivity C-reactive protein (DAS28-CRP) at Week 12 for GP2017 (Table 3).[18] Noteworthy, ABP 501 presented statistically significant superiority over reference drug in ACR20 responses at Weeks 2 and 12, but not at other time points or secondary efficacy endpoints.[30,31] This was

not considered by the regulatory agencies to compromise biosimilarity and was attributed to chance. Secondary efficacy endpoints, including ACR50/70 responses, European League Against Rheumatism (EULAR) criteria responses, and DAS28 variations and remission were also similar between reference drug and biosimilar candidates.[18,22,24,26-28] Interestingly, in pivotal trials of adalimumab biosimilars, a slightly higher proportion of patients in both biosimilar and reference arms achieved the ACR20 primary endpoint compared to the active arm in pivotal trials of originator adalimumab, which may be attributed to different trial designs.[32]

Table 2: Phase I clinical trials for each approved adalimumab biosimilar.

Biosimilar	Trial phase	Population	N	Primary endpoint	Results
ABP 501	Phase I[16]	Healthy subjects	203	PK bioequivalence of ABP 501 and USA and EU-ADL, as assessed by AUCinf and Cmax; equivalence margin 0.80–1.25	**EFFICACY:** ABP 501/USA-ADL: AUCinf 1.11 (90% CI: 1.00–1.24); Cmax 1.04 (90% CI: 0.96–1.12); ABP 501/EU-ADL: AUCinf 1.04 (90% CI: 0.94–1.17); Cmax 0.96 (90% CI: 0.89–1.03); USA-ADL/EU-ADL: AUCinf 0.94 (90% CI: 0.84–1.04); Cmax 0.92 (90% CI: 0.860–0.994) **SAFETY:** **Any TEAE** ABP 501: 58.2%, USA-ADL: 47.8%, EU-ADL: 68.7% **Any serious AE** ABP 501: 0.0%, USA-ADL: 0.0%, EU-ADL: 1.5%* *Was considered unrelated to the study drug
SB5	Phase I[17]	Healthy subjects	189	PK bioequivalence of SB5 and EU-ADL, USA-ADL as assessed by AUCinf, AUC last, and Cmax; equivalence margin 0.80–1.25	**EFFICACY:** SB5/USA-ADL: AUCinf 1.001 (90% CI: 0.890–1.126); AUClast 1.025 (90% CI: 0.911–1.153); Cmax 0.972 (90% CI: 0.881–1.073) SB5/EU-ADL: AUCinf 0.990 (90% CI: 0.885–1.108); AUClast 1.027 (90% CI: 0.915–1.153); Cmax 0.957 (90% CI: 0.870–1.504) USA-ADL/EU-ADL: AUCinf 1.011 (90% CI: 0.904–1.131); AUClast 0.998 (90% CI: 0.887–1.122); Cmax 1.016 (90% CI: 0.920–1.121) **SAFETY:** **Any TEAE** SB5: 57.1%, USA-ADL:61.9%, EU-ADL: 46.0% **Any serious AE** SB5: 1.6%,* USA-ADL: 1.6%,* EU-ADL: 0.0% *Were considered unrelated to the study drug
GP2017	Phase I[18]	Healthy subjects	318	PK bioequivalence of GP2017 and EU-ADL, USA-ADL as assessed by AUCinf and Cmax; equivalence margin 0.80–1.25	**EFFICACY:** GP2017/EU-ADA: AUCinf 1.04 (90% CI: 0.96–1.13); Cmax 1.05 (90% CI: 0.99–1.11) EU-ADA/USA-ADA: AUCinf 1.04 (90% CI: 0.96–1.13); Cmax 0.95 (90% CI: 0.90–1.01) **SAFETY:** **Any TEAE** GP2017: 62.7%, ADL: 73.9% **Any serious AE** GP2017: 0.3%;* ADL: 0.3%† *Was suspected to be related to the study drug †Was considered unrelated to the study drug

Table 2 continued.

Biosimilar	Trial phase	Population	N	Primary endpoint	Results
BI 695501	Phase I (VOLTAIRE-PK)[19]	Healthy subjects	327	PK bioequivalence of BI 695501 and USA and EU-ADL as assessed by AUCinf, AUClast, and Cmax; equivalence margin 0.80–1.25	**EFFICACY** BI 695501/USA-ADL: AUCinf 108.6% (90% CI: 98.5–119.8%); AUClast 107.3% (90% CI: 98.5–117.0%); Cmax 100.9% (90% CI: 95.2–106.9%) BI 695501/EU-ADL: AUCinf 101.3% (90% CI: 92.5–111.0%); AUClast 99.9% (90% CI: 92.2–108.4%); Cmax 96.4% (90% CI: 91.1–102.0%) USA/EU-ADL: AUCinf 94.0% (90% CI: 86.0–102.8%); AUClast 93.7% (90% CI: 86.8–101.1%); Cmax 95.9% (90% CI: 90.8–101.3%) **SAFETY** **Any TEAE** BI 695501: 19.4%, USA-ADL: 26.9%, EU-ADL: 25.9% **Any serious AE** BI 695501: 2.8%, USA-ADL: 2.8%, EU-ADL: 1.9% Of these, two serious AE (abdominal pain in the BI 695501 group and appendicitis in the USA-approved Humira group) were considered related to the study drug
FKB327	Phase I[20]	Healthy subjects	180	PK bioequivalence of FKB327 and USA and EU-ADL as assessed by AUCinf and Cmax; equivalence margin 0.80–1.25	**EFFICACY** FKB327/USA-ADL: AUCinf 0.98 (90% CI: 0.88–1.10); AUClast 1.01 (90% CI: 0.91–1.12); Cmax 1.07 (90% CI: 0.98–1.17) FKB327/EU-ADL: AUCinf 1.06 (90% CI: 0.94–1.18); AUClast 108 (90% CI: 0.97–1.20); Cmax 1.13 (90% CI: 1.03–1.23) USA/EU-ADL: AUCinf 0.93 (90% CI: 0.83–1.04); AUClast 0.93 (90% CI: 0.84–1.03); Cmax 0.95 (90% CI: 0.87–1.04) **SAFETY** **Any TEAE** FKB327: 58.3%, USA-ADL: 60.0%, EU-ADL: 65.0% **Any serious AE** FKB327: 1.7%,* USA-ADL: 1.7%,* EU-ADL: 0.0% *Possibly related to the study drug
MSB11022	Phase I[21]	Healthy subjects	213	PK bioequivalence of MSB11022 and USA-ADL and EU-AD as assessed by Cmax, AUCinf, and AUClast; equivalence margin 0.80–1.25	**EFFICACY** MSB11022/USA-ADL: AUCinf 90.46% (90% CI: 81.29–100.67%); AUClast 96.03% (90% CI: 85.32–108.88%); Cmax 97.22% (90% CI: 89.27–105.88%) MSB11022/EU-ADL: AUCinf 89.12 (90% CI: 80.14–99.10%); AUClast 91.53% (90% CI: 81.33–103.02%); Cmax 95.38% (90% CI: 87.58–103.87%) USA/EU-ADL: AUCinf 98.52% (90% CI: 88.56–109.59%); AUClast 95.32% (90% CI: 84.72–107.25%); Cmax 98.10% (90% CI: 90.11–106.81%) **SAFETY** **Any TEAE** MSB11022: 62.8%, USA-ADL: 56.3%, EU-ADL: 62.0% **Any serious AE** MSB11022: 2.6%,* USA-ADL: 0.0%, EU-ADL: 0.0% *Were considered unrelated to the study drug

AE: adverse event; AUCinf: concentration time curve (AUC) from time 0 extrapolated to infinity; AUClast: concentration time curve (AUC) from time 0 extrapolated to last quantifiable concentration; CI: confidence interval; Cmax: maximum (peak) serum concentration; EU-ADL: European Union-sourced adalimumab; PK: pharmacokinetic; TEAE: treatment emergent adverse event; USA-ADL: United States of America-sourced adalimumab.

Table 3: Phase III clinical trials for each approved adalimumab biosimilar.

Biosimilar	Trial phase	Population	N	Primary endpoint	Results
ABP 501	Phase III[22]	Moderate-to-severe active RA despite MTX	526	Therapeutic equivalence in ACR20 responses at Week 24; equivalence margin 0.738–1.355	**EFFICACY** ACR20 response at Week 24 was 74.6% (ABP 501) and 72.4% (ADL); risk ratio of ACR20 (90% CI) between groups was 1.039 (0.954, 1.133) **SAFETY** **Any TEAE** ABP 501: 50.0%, ADL: 54.6% **Any serious AE** ABP 501: 3.8%, ADL: 5.0% **IMMUNOGENICITY** Baseline **ADAb:** ABP 501: 1.9%; ADL: 2.3%; nAb: ABP 501: 0.0%, ADL: 0.0% Week 4, 12, or 26 **ADAb:** ABP 501: 38.3%; ADL: 38.2%; nAb: ABP 501: 9.1%, ADL: 11.1%
	Phase III[23]	Moderate-to-severe chronic plaque-type psoriasis	350	Therapeutic equivalence in PASI improvement at Week 16 (equivalence margin of ±15); PASI 50, PASI 75, PASI 90, and PASI 100 responses, sPGA response and mean change in affected BSA from baseline at Weeks 16, 32, and 50 after re-randomisation	**EFFICACY** PASI percent improvement at Week 16 was 80.9% (ABP 501) and 83.1% (ADL) (least-square mean difference −2.18 [95% CI: −7.39 to 3.02]); after re-randomisation, PASI percent improvement at Week 32 was 87.6% (ABP 501/ABP 501), 88.2% (ADL/ADL), and 87.0% (ADL/ABP 501); at Week 50 was 87.2% (ABP 501/ABP 501), 88.1% (ADL/ADL), and 85.8% (ADL/ABP 501) sPGA at Week 16 was 66.4% (ABP 501/ABP 501), 73.4% (ADL/ADL), and 67.5% (ADL/ABP 501); at Week 32 was 66.4% (ABP 501/ABP 501), 72.2% (ADL/ADL), and 70.4% (ADL/ABP 501); and at Week 50 was 68.7% (ABP 501/ABP 501), 74.3% (ADL/ADL), and 69.6% (ADL/ABP 501) BSA affected at Week 16 of -19.3% (ABP 501/ABP 501), -24.2% (ADL/ADL), and -23.5% (ADL/ABP 501); Week 32 and 50 BSA results were similar to those at Week 16 and percentages for each group at all time points were comparable **SAFETY** Week 16 **Any TEAE** ABP 501: 67.2%, ADL: 63.6% **Any serious AE** ABP 501: 3.4%, ADL: 2.9% Week 50 **Any TEAE** ABP 501/ABP 501: 71.1%, ADL/ADL: 65.8%, ADL/ABP 501: 70.1% **Any serious AE** ABP 501/ABP 501: 2.6%, ADL/ADL: 5.1%, ADL/ABP 501: 5.2% **IMMUNOGENICITY** Any time point throughout Week 52 **ADAb:** ABP 501/ABP 501: 68.4%, ADL/ADL 74.7%, ADL/ABP 501: 72.7%; **nAb:** ABP 501/ABP 501: 13.8%, ADL/ADL 20.3%, ADL/ABP 501: 24.7%

Table 3 continued.

Biosimilar	Trial phase	Population	N	Primary endpoint	Results
SB5	Phase III[24]	Moderate-to-severe active RA despite MTX	542	Therapeutic equivalence in ACR20 responses at Week 24; equivalence margins of ±15%	**EFFICACY** ACR20 response at Week 24 was 72.4% (SB5) and 72.2% (ADA); adjusted difference (SB5–ADL) was 0.1% (95% CI: -7.83–8.13%) **SAFETY** **Any TEAE** SB5: 35.8%, ADL: 40.7% **Any serious AE** SB5: 1.1%, ADL: 2.9% **IMMUNOGENICITY** Up to Week 24 **ADAb:** SB5: 33.1%; ADL: 32.0%; **nAb:** SB5: 16.5%, ADL: 16.0% Week 24 **ADAb:** SB5: 32.4%, ADL: 31.4%; **nAb:** SB3: 13.6%, ADL: 14.6%
GP2017	Phase III[18]	Moderate-to-severe active RA despite MTX	353	Therapeutic equivalence in DAS28-CRP responses at Week 12; equivalence margin of ±0.6	**EFFICACY** Mean change from baseline at Week 12 in DAS28-CRP was -2.16% for GP2017 (n=140) and -2.18% for ADL (n=144) (Δ=0.02; 95% CI: -0.24, 0.27) **SAFETY** **Any TEAE** GP2017: 61.6%, ADL: 60.2% **Any serious AE** GP2017: 1.7%, ADL: 1.7% **IMMUNOGENICITY** Week 24 **ADAb:** GP2017: 21.8%, ADL: 24.4%; **nAb:** GP2017: 75%, ADL: 73.2%
	Phase III[25]	Moderate-to-severe chronic plaque-type psoriasis	448	Therapeutic equivalence in PASI75 response rate at Week 16; equivalence margin of ±18%	**EFFICACY** PASI75 response at Week 16 was 58.1% (GP2017) and 55.9% (ADA); adjusted difference (GP2017–ADL) was 2.2% (95% CI: -6.79–11.10) **SAFETY** **Any TEAE** GP2017: 61.3%; ADL: 64.9% **Any serious AE** GP2017: 0.0%; ADL: 0.4% **IMMUNOGENICITY** Baseline **ADAb:** GP2017: 1.3%, ADL: 1.3%; **nAb:** GP2017: 0.0%, ADL: 0.0% Week 17 **ADAb:** GP2017: 25.7%, ADL: 26.7%; **nAb:** GP2017: 95.8%, ADL: 97.7%

Table 3 continued.

Biosimilar	Trial phase	Population	N	Primary endpoint	Results
BI 695501	Phase III (VOLTAIRE-RA)[26]	Moderate-to-severe active RA despite MTX	645	Therapeutic equivalence in ACR20 responses at Weeks 12 (equivalence margin: -12%–15%) and 24 (equivalence margin: ± 15%)	**EFFICACY** ACR responses at Week 12: 67.0% (BI 695501) and 61.1% (ADL) (90% CI: -0.9–12.7); ACR responses at Week 24: 69.0% (BI 695501) and 64.5% (ADL) (95% CI: -3.4–12.5) **SAFETY** **Any TEAE** BI 695501/BI 695501: 19.1%, ADL/BI 695501: 19.2%, ADL/ADL: 22.9% **Any serious AE** BI 695501/BI 695501: 5.6%, ADL/BI 695501: 6.8%, ADL/ADL: 9.7% **IMMUNOGENICITY** Week 24 **ADAb:** BI 695501: 1.70%, ADL: 3.28%; **nAb:** BI 695501: 1.4%, ADL: 2.5% Week 48 **ADAb:** BI 695501: 47.4%, ADL: 53.0%; **nAb:** Frequencies up to Week 24 were also similar between the groups
FKB327	Phase III[27]	Moderate-to-severe active RA despite MTX	728	Therapeutic equivalence in ACR20 responses at Weeks 24; equivalence margin ±13%	**EFFICACY** ACR20 responses at Week 24: 74.4% (FKB327) and 75.7% (ADL); (95% CI: -7.6–5.0) **SAFETY** **Any TEAE** FKB327: 55.5%, ADL: 61.6% **Any serious AE** FKB327: 4.1%, ADL: 5.2% **IMMUNOGENICITY** Baseline **ADAb:** FKB327: 3.7%, ADL: 5.3%; **nAb:** FKB327: 2.5%, ADL: 61.1% Week 24 **ADAb:** FKB327: 62.0%, ADL: 59.4%; **nAb:** FKB327: 4.4%, ADL: 59.1%
MSB11022	Phase III[28]	Moderate-to-severe chronic plaque-type psoriasis	443	Therapeutic equivalence in PASI75 response rate at Week 16; equivalence margin of ±18%	**EFFICACY** PASI75 response at Week 16 was 90.6% (MSB11022) and 91.7% (ADA); adjusted difference (MSB11022–ADL) was 1.0% (95% CI: -1.23–2.98) **SAFETY** **Any TEAE** MSB11022: 51.1%, ADA: 53.2% **Any serious AE** MSB11022: 3.6%, ADA: 2.7% **IMMUNOGENICITY** Week 24 **ADAb:** MSB11022: 87.3%, ADL: 88.6%; **nAb:** MSB11022: 37.6%, ADL: 39.1%

ACR20: American College of Rheumatology 20% improvement criteria; ADAb: antidrug antibody; ADL: adalimumab; AE: adverse event; BSA: body surface area; CI: confidence interval; DAS28-CRP: disease activity score-28 including high-sensitivity C-reactive protein; MTX: methotrexate; nAb: neutralising antibody; PASI: Psoriasis Area and Severity Index; RA: rheumatoid arthritis; sPGA: static Physician's Global Assessment; TEAE: treatment emergent adverse event.

MSB11022 performed similarly to reference drug in Psoriasis Area and Severity Index (PASI) 75 response at Week 16 (primary endpoint) in a Phase III trial in plaque-type psoriasis, confirming biosimilarity.[28] This biosimilar was recently assessed in a Phase III trial of RA patients but results were not available to this date. ABP 501 and GP2017 also had Phase III trials in plaque-type psoriasis, showing comparable results in primary (PASI percent improvement and PASI 75, respectively) and secondary endpoints at Week 16.[23,25]

Despite being assessed in trials of patients with RA and psoriasis, approved adalimumab biosimilars were granted by the regulatory agencies with the remaining clinical indications of the originator drug (extrapolation of indications).

Safety

No new adverse events were found in Phase III clinical trials beyond those expected for the population and drug class, and the majority were classified as mild-to-moderate in severity.

The rate of treatment-emergent adverse events (TEAE) was similar in the biosimilar and reference drug groups, ranging from 19.1–61.6% for biosimilars (ABP 501: 50.0%, SB5: 35.8%, GP2017: 61.6%, BI 695501: 19.1%, FKB327: 55.5%, MSB11022: 58.0%) and 40.7–62.0% for reference adalimumab.[18,22,24,26-28] The rate of severe adverse events was also similar in both groups, ranging from 1.1–5.6% for the biosimilar group (ABP 501: 3.8%, SB5: 1.1%, GP2017: 1.7%, BI 695501: 5.6%, FKB327: 4.1%, MSB11022: 3.6%) and 1.7–5.0% for the reference drug group.[18,22,24,26-28]

Despite similar safety profiles, some minor differences are worth mentioning. For instance, ABP 501, BI 695501, and SB5 had fewer injection site reactions compared to reference adalimumab,[22,24,26] which was considered not relevant and attributed to differences in excipients by regulatory agencies. BI 695501 showed increased incidence of analytical changes like anaemia (most in patients with low haemoglobin levels at baseline); bone fractures (but incidence within expected range in the general population); and positive screening for tuberculosis (no active cases). EMA accepted these events as rare and attributed to chance.[33]

Immunogenicity

The use of a biologic agent can trigger an immune response, which may result in reduced efficacy, treatment failure, or adverse effects.[34] Detailed immunogenicity evaluations are required for approval of biosimilars and the types of assays and sensitivity of detection are described in updated regulatory guidance documents.[35,36] In the case of rheumatic diseases, 25 studies with immunogenicity data for 16 biosimilars or biosimilar candidates are published: 7 with adalimumab as the reference product (biosimilars BI 695501, SB5, ABP 501, FKB327, and MSB11022, and biosimilar candidates PF-06410293 and ZRC-3197).

Studies of adalimumab in both healthy volunteers and patients varied in methodology of antidrug antibodies (ADAb)/neutralising antibodies (nAb) detection, as well as study design and duration, meaning that comparisons between studies are not a reliable means to determine which biosimilar is more prone to elicit an immune response. Nevertheless, immunogenicity results of Phase III trials are summarised in Table 3.

The incidences of ADAb in adalimumab trials generally increased with trial duration (reaching a plateau after 12–24 weeks of treatment), a phenomenon that was not observed in trials of etanercept, rituximab, and their biosimilars. Typically, ADAb-positive individuals had lower drug concentrations and higher clearance rates compared with ADAb-negative individuals, with effects comparable between reference products and biosimilars. Overall, in adalimumab trials there is evidence that the formation of ADAb is associated with deterioration in certain pharmacodynamic parameters such as CRP or erythrocyte sedimentation rate and diminished clinical efficacy and safety, but the statistical significance of those differences was generally not examined in individual trials.

Cross-reactivity assessments show the ability of ADAb to bind both the reference and biosimilar products and have been reported in only four randomised control trials in rheumatic diseases, one of them with adalimumab and its biosimilar FKB327.[20]

Biosimilars can be introduced into patients' treatment regimens, which may affect immunogenicity. Available data for the biosimilars

of adalimumab indicate that switching resulted in no changes in quantitative or qualitative immunogenicity (see below). Overall, the ranges of ADAb incidences in pivotal randomised control trials of reference products are lower than those reported in recent trials comparing them to their biosimilars,[37] which may be a result of improvements in assay methodology (including sample handling, drug trough levels, validation techniques, sample storage, number of replicates), sensitivity (currently mandated by regulatory agencies),[35,36] as well as patient disease status and the trial design employed.[38]

Switch

All adalimumab biosimilars have information on at least one switch, except MSB11022. Their Phase III clinical trials were extended to a later period of evaluation where patients on the reference drug were re-randomised to switch to biosimilar or to remain on reference drug. These studies had on average a post-switch period of 28 weeks (ABP 501 [psoriasis]: Week 16 to 52; GP2017 [RA]: Week 24 to 48; BI 695501: Week 24 to 48; SB 5: Week 24 to 52; FKB327: Week 28 to 48). ACR20/50/70 response rates and mean change from baseline in DAS28-erythrocyte sedimentation rate were similar across the switched and the continuous groups.[18,22-27]Also, there were no differences in the rate of treatment discontinuation between groups. In the study of SB5, radiographic results were also analysed. Radiographic progression was comparable between all treatment groups over the course of 52 weeks, and consistent with historical data for reference adalimumab.[39] Whilst these studies assessed a single transition from reference to biosimilar drug, GP2017 had a Phase III trial performed in patients with chronic plaque-type psoriasis including a multiple-switch period.[25] Patients achieving a ≥50% PASI improvement were re-randomised to maintain their originally assigned treatment or to receive either GP2017 or reference adalimumab during three alternating 6-week periods. Once again, no significant difference in efficacy, safety, or immunogenicity was found between switchers and non-switchers.[25]

With regard to safety, the different clinical trials also showed similar results between switch and maintenance groups. The rate of TEAE was similar in these groups, ranging from 15.6–54.6% for switch groups (adalimumab to SB5: 37.6%' adalimumab to GP2017 [RA]: 45.5%, adalimumab to BI 695501: 42.5%; adalimumab to FKB327: 54.6%; adalimumab to ABP5 01 [psoriasis]: 15.6%; adalimumab to GP2017 [psoriasis]: 46.0%), 19.0–55.9% for the adalimumab maintenance groups, and 23.0–53.1% for the biosimilar maintenance groups. The rate of severe adverse events was also similar, ranging from 0.0–5.7% for the switch groups (adalimumab to SB5: 3.2%; adalimumab to GP2017 [RA]: 5.7%; adalimumab to BI 695501: 4.1%; adalimumab to FKB327: 2.8%, adalimumab to ABP 501 [psoriasis]: 0.0%; adalimumab to GP2017 [psoriasis]: 6.0%), 0.0–6.3% for the adalimumab maintenance groups, and 1.3–4.0% for the biosimilar maintenance groups. No hypersensitivity to adalimumab was reported upon switching.[18,22-27]

Switch data on adalimumab biosimilars are reassuring but should be interpreted with caution, as most trials assessed a single transition in a small number of patients with limited follow-up periods. Further evidence from pharmacovigilance programmes and real-world studies will be necessary to properly assess interchangeability of adalimumab biosimilars.

PHARMACOECONOMICS OF ADALIMUMAB BIOSIMILARS

The bio-originator adalimumab has proven efficacy and safety in the treatment of rheumatic, ophthalmic, dermatological, and gastroenterological conditions. This therapeutic versatility has made adalimumab the top-selling drug worldwide since 2012.[1] In 2017 alone, sales reached $18.43 billion for all clinical indications.[1] Naturally, expectations are high for the potential cost savings from adalimumab biosimilars and their role in the reduction of the economic burden of biotherapies.

A recently published article by Aladul et al.[40] assessed the effect of the introduction of infliximab, etanercept, and adalimumab biosimilars in rheumatology and gastroenterology specialities on UK healthcare budget. The budget impact model built for adalimumab assumed a 33% price discount for the biosimilar drug in the first year and an annual 15% discount up to the fourth year, as well as price erosion of the reference drug reaching 50% at this latter time point. From 2017 to 2020, considering an annual

growing market share of 10%, 35%, 60%, and 90%, savings due to Solymbic® (Amgen, USA), Amgevita® (Amgen, USA), and Imraldi® (Biogen, South Korea) are expected to reach £177 million and £91 million in rheumatic and inflammatory bowel diseases, respectively.[40] Two other analyses were published as abstracts. The first used data from a USA claims-base and estimated annual combined savings of $6.1 million per 10,000 insured RA patients treated with infliximab or adalimumab biosimilars (assuming a 30% market share and 25% price discount).[41] The second estimated combined savings over 1 year of €26 million, €351 million, and €98 million in France, Germany, and the UK, respectively, with the use of infliximab, etanercept, or adalimumab biosimilars in RA patients (assuming a 50% biosimilar quota and 30% price discount).[42]

Overall, budget impact analyses of adalimumab biosimilars are still scarce, especially when compared to infliximab and etanercept biosimilars. Based on what is known from these therapies, cost savings generated by adalimumab biosimilars will allow thousands of new patients to be treated every year (assuming these savings are re-invested) and will play an important role in the sustainability of healthcare systems worldwide.[43]

CONCLUSION

All currently approved adalimumab biosimilars have demonstrated equivalence to reference product in preclinical and clinical studies and have been rigorously scrutinised by regulatory agencies before approval. Further reassurance on the safety and efficacy of adalimumab biosimilars in clinically studied and extrapolated indications will come from mandatory long-term pharmacovigilance programmes established by the FDA and EMA, as well as real-world data from national patient registries. The worldwide success of bio-originator adalimumab will grant its biosimilars an economic impact that will surpass the one seen with infliximab, etanercept, or rituximab, further contributing to the treatment sustainability of patients with immune-mediated inflammatory conditions.

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Real-World Experience of Apremilast in Treating Psoriatic Arthritis Patients with Comorbidities

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Abstract

This observational study aimed to evaluate the efficacy and real-world experience of apremilast (APR) in treating psoriatic arthritis (PsA) patients with co-existing conditions presenting to clinic. Data from 28 patients treated with APR for PsA were collected between January 2016 and January 2019. Outcome measures disease activity score 44-C-reactive protein (DAS44-CRP), 0–68 for tender and 0–66 for swollen joint count, were collected at Weeks 0, 16, and 52. Response was classified using the Psoriatic Arthritis Response Criteria (PsARC). Adverse events or worsening of pre-existing conditions were recorded. Results included outcomes at Weeks 16 and 52 which showed a percentage reduction in mean DAS44-CRP at Weeks 16 and 52 by -1.4 and -1.9, respectively. There was percentage reduction at Weeks 16 and 52 of tender (-55.5%, -75.4%) and swollen (-45.8%, -61.5%) joint counts from baseline. It was also found that 19/28 (68.0%) patients were responders by PsARC criteria up to Week 52. Responders had shorter disease duration (mean: 4.9 years, standard deviation: 1.9) and lower previous exposure to biologic disease-modifying antirheumatic drugs (bDMARD); 16/19 subjects (84.0%) had no previous bDMARD. There were no serious adverse events during the study and no worsening of co-existing conditions during treatment. In this real-world observational study, APR was shown to be effective in PsA patients with multiple co-existing conditions. APR was more effective in PsA patients with shorter disease duration and in bDMARD naïve patients. APR provides another effective treatment option for PsA patients with multiple co-existing conditions.

INTRODUCTION

Apremilast (APR) is a small molecule phosphodiesterase-4 inhibitor that is used in the treatment of psoriasis (PsO) and psoriatic arthritis (PsA). Randomised controlled trials (RCT) have shown that APR is effective in both psoriasis and PsA.[1,2] The Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) RCT have shown APR to be effective in treating

PsA.[3-6] There is, however, limited real-world data on the use of APR in PsA.[7] The objective of this study is to report on the real-world experience and outcomes of using APR in PsA patients with co-existing conditions.

METHODS

The authors performed an observational study on the effectiveness and tolerability of APR at a standard dose of 30 mg twice a day, following a loading dose in patients with PsA. All subjects fulfilled classification criteria for PsA (CASPAR)[8] and had active disease according to the National Institute of Clinical Excellence (NICE) criteria for treatment with APR in PsA.[9] Patients meeting the NICE criteria who were deemed suitable by the attending rheumatologist were commenced on APR. This study was an evaluation of standard clinical practice and outcome of APR use against NICE criteria and, as such, ethical approval was not required.

As part of the NICE guidance, PsA patients were assessed at baseline, at 16 weeks, and every 6 months. Clinical assessments at each visit included the disease activity score 44-C-reactive protein (DAS44-CRP), scoring for tender joints (0–68), swollen joint count (0–66), CRP levels, and patient and physician global assessments on a 5-point Likert scale. High disease activity is defined as a DAS44 of >3.7, moderate activity is defined as a DAS44 between 2.4 and 3.7, low activity is defined as a DAS44 between ≤2.4 and ≥1.6, and remission is defined as a DAS44 <1.6. Efficacy outcomes were recorded at the assessment at Weeks 16 and 52 and compared with the baseline evaluation. The PsA response criteria (PsARC) was calculated and subjects were defined as responders if there was an improvement in at least two of the four PsARC criteria (including joint tenderness or swelling score) with no worsening in any criteria.[10] Subjects were classified as responders and non-responders based on the PsARC status up to Week 52. In non-responders who stopped APR at Week 16, this was the last observation measured. Patients who stopped APR between Weeks 16 and 52 were excluded from further analysis at Week 52.

STATISTICAL ANALYSIS

Continuous variables were expressed as median (range) or mean (standard deviation [SD]) as appropriate and binomial variables were expressed as number and percentage. The data followed a normal distribution and comparisons between baseline and follow-up measurements were performed using paired Student's t-test with significance of the difference set at $p<0.05$. Significant differences between responders and non-responders were defined as those at a level of $p<0.05$ by either Student's t-test or Chi-squared test.

RESULTS

A total of 28 PsA patients (n=16 [57.1%] female, n=12 [42.9%] male) attending the rheumatology clinic between January 2016 and January 2019, who were deemed suitable for APR based on NICE criteria, were included in this study. The patients started on APR within this study had active PsA (>3 tender and >3 swollen joints) and with previous failure to a minimum of two conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARD). The mean age was 53 (SD: 11) years and the mean PsA disease duration 5.9 (SD: 2.5) years. Mean number of csDMARD pre-APR was three. Of the patients in this study, 11 (40.0%) were biologic (b)DMARD inadequate responders prior to commencing APR. No patients had targeted synthetic DMARD prior to commencing APR. Clinical characteristics are shown in Table 1.

The mean DAS44-CRP was measured at baseline and at Weeks 16 and 52. The baseline DAS44-CRP was 3.8 (SD: 0.7). Patients had active PsA with the mean DAS44-CRP >3.7 at baseline. The mean DAS44-CRP was reduced at Weeks 16 (-1.4, SD: 1.0) and 52 (-1.9, SD: 1.1) (Figure 1). The difference in DAS44-CRP at Weeks 16 and 52 compared to baseline was statistically significant $p<0.01$. Four patients stopped APR at Week 16 due to inefficacy. Two patients stopped APR between Weeks 16–52 (mean: 31.9, SD: 3 weeks). The tender and swollen joint counts were recorded at baseline and at follow up. There was a percentage reduction at Weeks 16 and 52 of mean tender (-55.5% and -69.3%) and mean swollen (-45.8% and -55.1%) joint counts

(Figure 2). The reduction in joint counts at Weeks 16 and 52 compared to baseline was clinically significant and reached statistical significance of p<0.01.

Based on the PsARC, 19 of 28 (68.0%) patients were classified as responders and 9 (32.0%) as non-responders up to Week 52 of this study. Subjects that stopped APR during this study were classified as non-responders. Responders had a shorter disease duration (mean: 4.9, SD: 1.9 years) compared to non-responders (mean: 7.3, SD: 2.3 years). This was statistically significant at p<0.05. All patients had prior exposure to csDMARD. Responders had lower exposure to bDMARD with 16 of 19 (84.2%) responders being bDMARD naïve compared to non-responders with 8 of 9 (88.9%) being bDMARD experienced. This association was statistically significant (p<0.01). There was no significant difference in age: responders had a mean age of 50.7 (SD: 12 years)and non-responders had a mean age of 55.4 (SD: 8.5 years; p=0.48).

Table 1: Baseline patient characteristic of 28 psoriatic arthritis patients treated with apremilast.

Baseline Patient Characteristics	Apremilast 30 mg bd
Age, mean (SD), years	53.0 (11.0)
Female, n (%)	16.0 (57.1)
Male, n (%)	12.0 (42.9)
PsA duration, mean (SD) years	5.9 (2.5)
TJC (0–68), mean (SD)	15.0 (8.0)
SJC (0–66), mean (SD)	9.0 (4.0)
DAS44-CRP, mean (SD)	3.8 (0.7)
Number of subjects with prior csDMARD use, n (%)	28.0 (100.0)
Number of csDMARD, mean (SD)	2.8 (1.0)
Number of subjects with prior bDMARD use, n (%)	11.0 (40.0)
Co-existing conditions	
Malignancy, n (%)	6.0 (21.4)
Multiple sclerosis, n (%)	2.0 (7.0)
Bronchiectasis, n (%)	4.0 (14.3)
Interstitial lung disease, n (%)	2.0 (7.0)
Hypertension, n (%)	9.0 (32.0)
Peripheral vascular disease, n (%)	2.0 (7.0)
Ischaemic heart disease, n (%)	5.0 (17.9)
Fibromyalgia, n (%)	9.0 (32.0)
Apremilast discontinuation, n (%)	9.0 (32.0)
Inefficacy	9.0 (32.0)
Diarrhoea	11.0 (39.0)
Nausea	6.0 (21.4)
Headache	5.0 (17.9)
Anxiety	3.0 (10.7)
General malaise	5.0 (17.9)

bd: twice daily; bDMARD: biologic disease-modifying antirheumatic drugs; csDMARD: conventional synthetic disease-modifying antirheumatic drug; DAAS44-CRP: disease activity score 44-C-reactive protein; PsA: psoriatic arthritis; SD: standard deviation; SJC: swollen joint count; TJC: tender joint count.

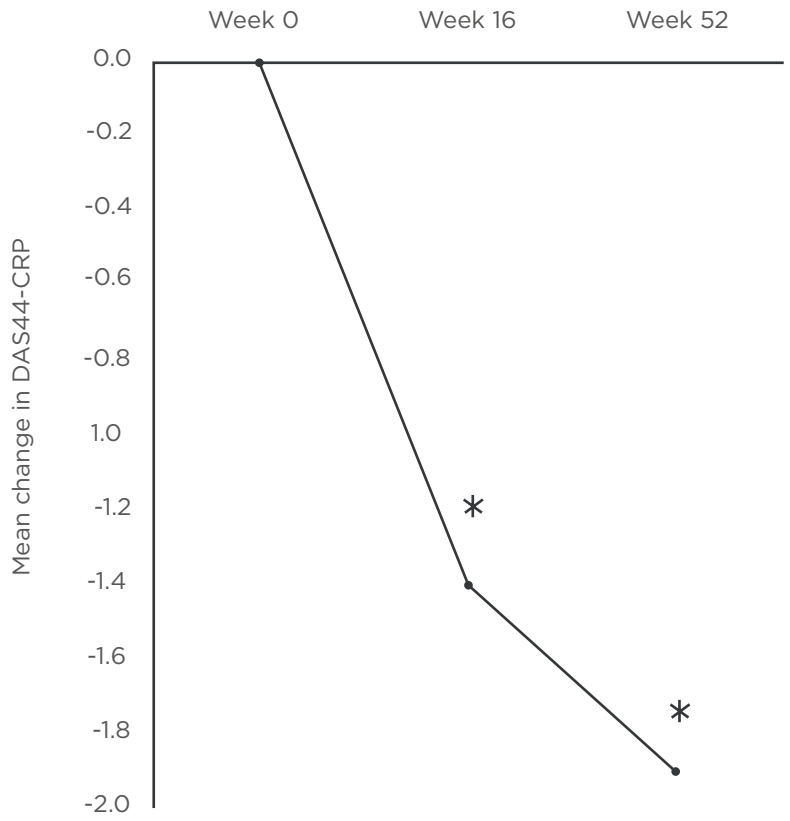

Figure 1: Mean change in disease activity score 44-C-reactive protein at Weeks 16 and 52 compared to baseline.

*p<0.01

DAS44-CRP: disease activity score 44-C-reactive protein.

There was also no significant difference in sex: 7 responders were male (37.0%) and 12 were female (63.0%), and non-responders were 5 males (56.0%) and 4 females (44.0%); p=0.35 was found between the responder and non-responder groups.

Comorbidity is defined as any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study.[11] In this study the prevalence of co-existing and comorbid conditions (Table 1) was included, including previous malignancy (6 patients, 21.4%). The types of cancer included breast (3 patients), lymphoma (1 patient), tongue (1 patient), and kidney (1 patient). The other co-existing conditions presented were multiple sclerosis (2 patients, 7.0%), bronchiectasis (4 patients, 14.3%), interstitial lung disease (2 patients, 7.0%), hypertension (9 patients, 32.0%), peripheral vascular disease (2 patients, 7.0%), ischaemic heart disease (5 patients, 17.9%), and fibromyalgia (9 patients, 32.0%). There was no worsening of co-existing conditions or any serious adverse events while on APR during the study up to 52 weeks. There was also no appreciable improvement in the comorbidities, such as cardiovascular disease or hypertension, during this study.

Of the 28 patients, 9 (32.0%) were discontinued after a mean treatment period of 7.3 months (SD: 3.6) due to lack of efficacy. In the first 52 weeks of APR treatment, the most common side effects were diarrhoea (11 patients, 39.0%) and nausea (6 patients, 21.0%). The gastrointestinal side effect did not necessitate stopping the medication. The other side effects were headache (5 patients, 17.9%), anxiety (3 patients, 10.7%), and general malaise (5 patients, 17.9%). None of these side effects necessitated stopping APR.

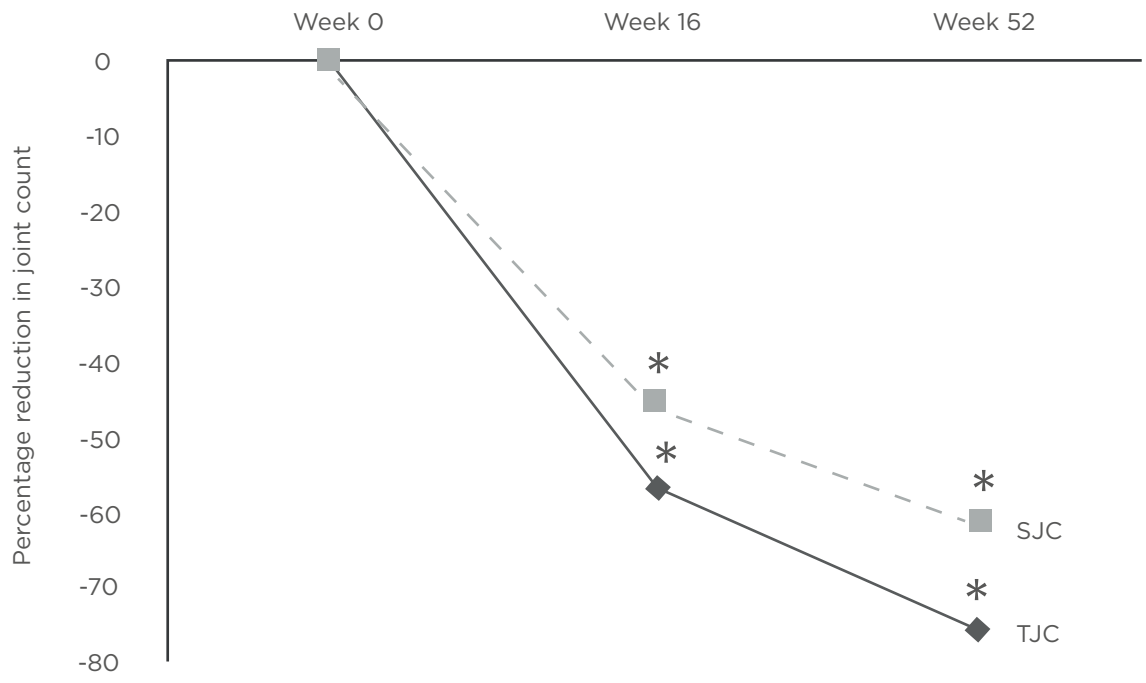

Figure 2: Mean percentage change in tender joint count and swollen joint count at Weeks 16 and 52 compared to baseline.

*p<0.01

SJC: swollen joint count; TJC: tender joint count.

DISCUSSION

Previously published RCT have shown that APR is effective in patients with PsA.[3-6] The RCT have also shown an acceptable safety profile of APR in the treatment of PsA. This study reports the real-world experience of the use of APR in unselected PsA patients with active disease. The presence of co-existing conditions in this patient cohort may mean that they could be excluded from clinical trials. There is limited real world data of APR use in PsA[7,12] It is therefore necessary to understand the real-world clinical experience of treating unselected PsA patients with multiple co-existing conditions in terms of its efficacy and side effects.

Pooled data from published RCT have shown a reduction in tender and swollen joint counts, as well as DAS28-CRP mean score.[3-6] This study also shows the efficacy of APR in treating unselected PsA patients in the clinic. All patients had at least two csDMARD according to the NICE guidance for treatment with APR[8] and thus this is applicable to most other clinics which follow this guidance. Patients with shorter duration of PsA and no previous exposure to bDMARD had a better response to APR. The finding of improved response in the bDMARD naïve group is also supported in a RCT.[13]

The limitations of this study are the small number of patients, lack of controls, and that it is not powered to show a difference in treatments. However, this is a real-world study and patients had a significant clinical improvement. Discontinuation of APR in this study was due to inefficacy based on failure to meet the PsARC target. Gastrointestinal side effects were common but did not necessitate stopping of APR. The other side effects were generally mild and self-limiting. There was no worsening of the underlying co-existing conditions or any serious adverse events during the course of treatment with APR. This is an important real world observation as there is increasing concern about the impact of treatments on co-existing conditions in patients with PsA such as obesity,[14] metabolic syndrome,[15] and cardiovascular disease.[16] Longerterm follow up of these patients

will inform the authors as to any benefits of these outcomes.

CONCLUSION

This study provides real-world clinic experience of the efficacy of APR in the treatment of active unselected PsA in patients with comorbidities. APR was tolerated and the efficacy was established in patients with PsA although they had other co-existing diseases, including cancer. APR improved the clinical outcomes over the first year of treatment compared to baseline. The response to APR was better in patients with shorter PsA duration and in bDMARD-naïve patients. There was an acceptable safety profile with no worsening of the comorbidities during the course of treatment. APR provides an additional treatment option for patients with active PsA. Further studies into its use in patients with multiple co-existing conditions will help determine its place in the treatment pathway for PsA.

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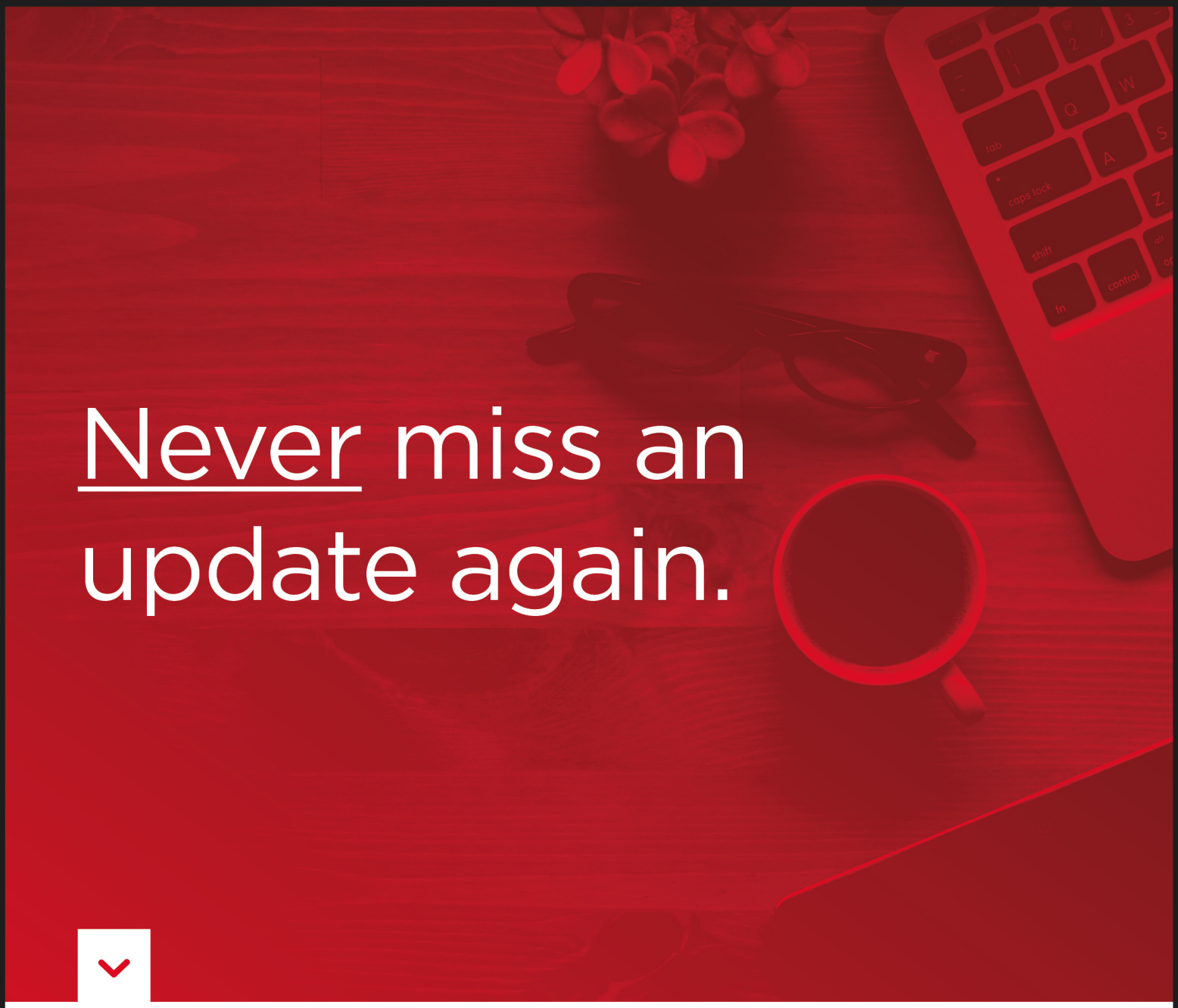

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