EMJ EUROPEAN MEDICAL JOURNAL

# RHEUMATOLOGY

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**INSIDE**
Review of
**EULAR 2016**
London, UK

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# RHEUMATOLOGY


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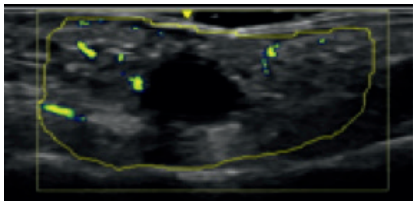

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# Welcome

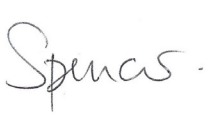
Welcome to *EMJ Rheumatology*. Here you will find the latest news and most important developments taking place in rheumatology. We are confident that the journal will prove to be both engaging and insightful for all readers, whether as a medical professional, an academic, an industry leader, or anyone interested in the field.

For 4 days in June this year, London was host to the 17th European League Against Rheumatism Congress (EULAR) Annual Congress of Rheumatology 2016. This was a fascinating and informative event that boasted the perfect forum to promote the ever-growing interest in rheumatic and musculoskeletal diseases. In the pages that follow we have included an extensive review of the latest news, research, and developments that came out of the congress for you to peruse.

Our abstract reviews have been provided directly by the researchers presenting at EULAR 2016 and raise pressing issues and important areas for discussion. This includes the value of immunosuppressive therapy, the effects of DNA methylation in association with osteoarthritis, and the role of the endocannabinoid system in immune-mediated diseases. Inside you can also find the latest news revealed at congress, with reports on childhood appendicitis and its reduction of the risk of arthritis later in life, and why oestrogen could be an effective hormonal therapy for systemic sclerosis.

As always, there are numerous high-quality, peer-reviewed articles for you to consider. This includes an insightful overview of extra-articular manifestations in rheumatoid arthritis patients, highlighting the seriousness of the problem for clinicians who are faced with its diagnostic difficulties and complex presentation. There is also an important discussion on idiopathic inflammatory myopathies and their association with overlap myositis and overlap syndromes. You can also read further on topics such as psoriatic arthritis, Sjögren's syndrome, and rheumatoid arthritis!

We sincerely hope that you enjoy this latest edition of *EMJ Rheumatology* and that you find it both valuable and influential in your own work in the field. Thank you for reading, and we look forward to sharing more discussions, insights, and developments with you in next year's edition.



**Spencer Gore**

*Director, European Medical Journal*

*European Medical Journal Rheumatology* is published annually.
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*Front cover and contents photograph: London, UK home of EULAR 2016.*

# HYPERURICEMIA WITH DEPOSITION: A SYSTEMIC DISEASE [1-2]


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1. Whelton A. et al. Journal of Clinical Rheumatology & Volume 17, Number 1, January 2011.
2.Tausche AK et al. Gout-current diagnosis and treatment. Dtsch Arztebl Int 2009;106:549-555.

# Foreword

**Dr Ian C. Chikanza**

*Consultant/Senior Lecturer in Adult and Paediatric Rheumatology, Department of Rheumatology, Barts Arthritis Centre, Barts and The Royal London Hospital, London, UK.*

Dear Colleagues and Friends,

Welcome to *EMJ Rheumatology*. In this issue we focus on the latest important developments taking place in rheumatology. We present focussed articles on idiopathic inflammatory myopathy and its association with overlap myositis and overlap syndromes; non-invasive cardiovascular imaging for cardiovascular risk assessment in rheumatoid arthritis and an insightful overview of extra-articular manifestations in rheumatoid arthritis patients; and TAM receptor tyrosine kinase signalling in Sjögren's syndrome and its potential as a therapeutic target in this disease. The therapeutic management of Sjögren's syndrome continues to be a challenge but current research is improving our understanding of the pathophysiologic mechanisms and opening therapy opportunities. The boundaries of rheumatology continue to be extended.

> "The therapeutic management of Sjögren's syndrome continues to be a challenge but current research is improving our understanding of the pathophysiologic mechanisms and opening therapy opportunities. The boundaries of rheumatology continue to be extended."

This year, London hosted the 17th Annual Congress of the European League Against Rheumatology (EULAR), a premium European rheumatology conference for physicians and scientists covering information on novel clinical research. This journal issue reviews and provides an insight into the fascinating developments in the field of rheumatology presented at the congress. The abstract reviews have been provided directly by the researchers presenting at EULAR 2016. These include the continuing value of immunosuppressive therapy, the effects of DNA methylation in osteoarthritis, and the role of the endocannabinoid system in immune-mediated diseases. The latest news from the congress also includes insights into childhood appendicitis and its potential reduction of the risk of arthritis later in life, and the immunomodulatory potential of oestrogen therapy in systemic sclerosis.

In conclusion, I am very pleased to present to you this third edition of *EMJ Rheumatology*. I sincerely hope that you will enjoy this latest issue and continue to find the content a positive and significant drive in your own thinking and work in the rheumatology field.

With kind regards,

**Ian C. Chikanza**

Consultant/Senior Lecturer in Adult and Paediatric Rheumatology, Department of Rheumatology, Barts Arthritis Centre, Barts and The Royal London Hospital, London, UK.


EXCEL

# **EULAR** ANNUAL CONGRESS 2016

EXCEL LONDON,
LONDON, UK
8TH-11TH JUNE 2016

## Welcome to the *European Medical Journal* review of the 17th EULAR Annual European Congress of Rheumatology

The bustling metropolis that is the city of London, UK was host to this year's EULAR congress. It is a city ranked by travellers as the top city destination in the world and it boasts the second highest number of international tourist arrivals in the world. Home to the pioneering English physician Sir Alfred Garrod who defined rheumatoid arthritis, London presents itself as an ideal location for this international meeting of leading rheumatologists from across the globe.

Attendance at the EULAR 2016 congress was around 14,000 people, travelling from over 100 countries to take part. More than 4,000 abstracts were submitted to the congress with 314 accepted as oral presentations. The congress hosted 200 sessions, nearly 2,000 poster displays, and 350 speakers. Together this reflects the significant interest surrounding research of rheumatic and musculoskeletal diseases (RMDs) while also establishing the EULAR congress as an informative venue for clinical research. In the opening ceremony, EULAR President Prof Gerd Burmester, Department of Rheumatology and Clinical Immunology, University Hospital Berlin, Berlin, Germany, was happy to comment on the popularity of the organisation. "[It is] encompassing of 45 nations and we are very proud of this; it ranges from Albania to the UK, from Croatia to Portugal," Prof Burmester said, "...[It] is a unique organisation because it is not just composed of medical doctors and scientists, we have health professionals and people with RMDs among us and jointly we tackle the disease you will hear about at this congress."

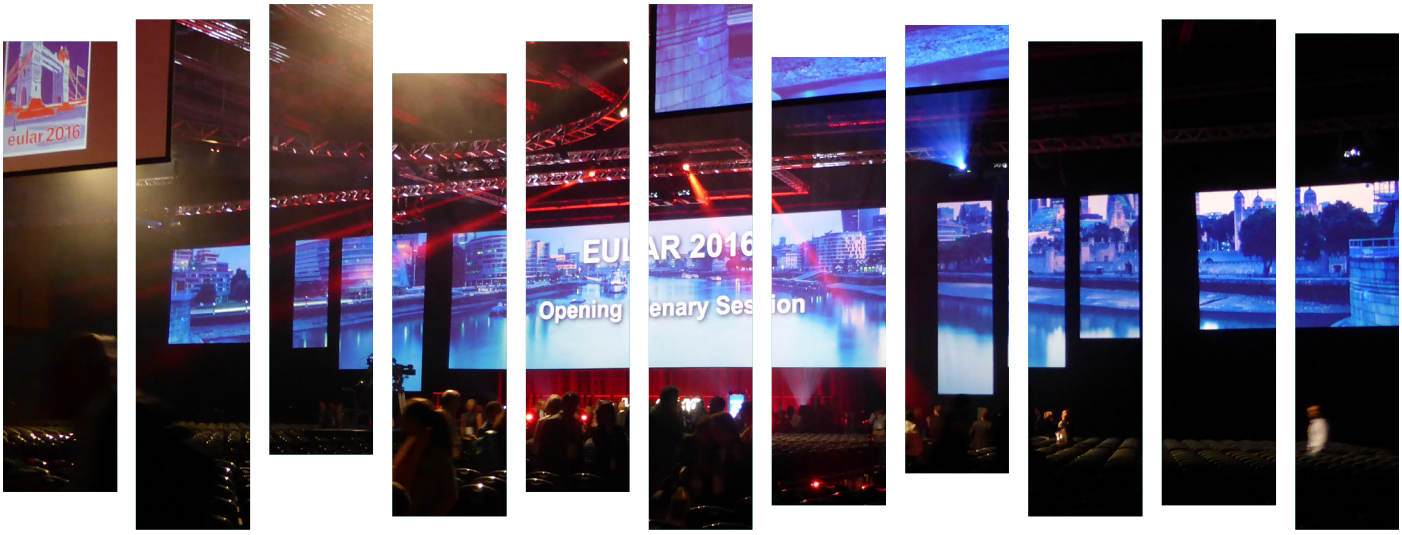
A range of awards were handed out at the congress in recognition of individuals who had submitted the best research in a number of areas. Among those recognised for the clinical abstracts there was Prof Athimalaipet Ramanan for demonstrating the superiority of the combination of adalimumab and methotrexate versus methotrexate alone in the treatment of juvenile idiopathic arthritis-associated uveitis. Dr Raquel Campanilho-Marques was recognised for her involvement in the largest study to research the efficacy and safety of tumour necrosis factor inhibitors for the treatment of juvenile dermatomyositis. Finally, Dr Uta Kiltz received the award on behalf of her research team whose work has confirmed the Assessment of Spondyloarthritis International Society

(ASAS) Health Index as a reliable measure of disease severity in spondyloarthritis. Also recognised at EULAR was basic science research looking at the pathogenesis of ankylosing spondylitis and the role of microRNA in juvenile Idiopathic arthritis. Wendy Olsder was recognised for her research and work in the field of people with arthritis/rheumatism in Europe where she has developed a guide for young people with rheumatological disease.

> “...[It] is a unique organisation because it is not just composed of medical doctors and scientists, we have health professionals and people with RMDs among us and jointly we tackle the disease you will hear about at this congress.”

For the fourth year in a row, EULAR also recognised undergraduate students for their involvement in clinical research. Nienke Conijn was among those who received an award for her work in the first study to examine the prevalence of asymptomatic gout in patients with Stage IV or Stage V chronic kidney disease. Aurélien Sokal was also recognised for his involvement in studying the outcomes of bisphosphonate exposure during pregnancy.

The standard of work presented at the congress was superb and the event proved an invaluable opportunity to explore the current research being undertaken in the field of rheumatology across Europe and beyond. The wide range of topics covered in these presentations included the role of nanotechnology for arthritis treatment, the use of genetic profiling to determine ineffective treatments, and the development of a new comordity index to better assess and manage psoriatic arthritis. As you will see in the following pages, these latest developments show us that the field of rheumatology continues to experience exciting advances and offers an optimistic outlook towards the continual improvement and management of RMDs.




## Discovery of a Genetic Link to Mouth Ulcers in Lupus Patients

A NEWLY discovered link between a specific genetic pathway and the development of mouth ulcers in patients with systemic lupus erythematosus (SLE) is an important step towards an increased understanding of the specific characteristics of the autoimmune disease. In a EULAR press release dated 10th June 2016, researchers have linked a polymorphism of the vascular endothelial growth factor (*VEGF*) gene with a particular distinguishing trait, mouth ulcers, in patients with the genetically complex SLE.

Although inflammation is characteristic of SLE, it often presents varying symptoms affecting multiple organ systems, frequently progressing to organ dysfunction and failure. Its outcome among individuals across different ancestral groups is highly dissimilar. The discovery of the link is considered important because it should lead to an improved understanding of the complexities of SLE. "Understanding the relationships between specific SLE risk genes and different manifestations of the disease should help elucidate the underlying disease mechanisms and pathways," Dr Antonio Julià Cano, Vall d'Hebron Research Institute, Barcelona, Spain, explained.

**Around 14,000 people**

A total of 598,258 single nucleotide polymorphisms were genotyped in a population of 482 Caucasian European SLE patients of Spanish origin. The researchers first tested 11 clinically relevant SLE phenotypes for association with over 700 reference genetic pathways. They found two genetic pathways to have a significant association with the presence of mouth ulcers and the presence of antinuclear antibodies found in SLE.

These two particular pathways were tested for validation in a second independent population of 425 SLE patients of the same Southern European ancestry and as before, a significant association between mouth ulcers and the *VEGF* pathway was confirmed. "Understanding more about the genetic pathways which underlie different manifestations of SLE is an important step towards the goal of improving

the management of SLE, and ultimately to offer preventative care to individuals at increased risk of SLE," said Dr Julià Cano.

## Polluted Air Linked to Increased Lupus Disease Activity

RESEARCHERS have pointed to a direct link between exposure to air pollution and both increased disease activity and airway inflammation in children and adolescents with systemic lupus erythematosus (SLE), according to a EULAR press release, 8th June 2016.

> "With air pollution increasing in many major cities, paediatric rheumatologists can expect to see a resultant impact on the disease activity of their lupus patients."

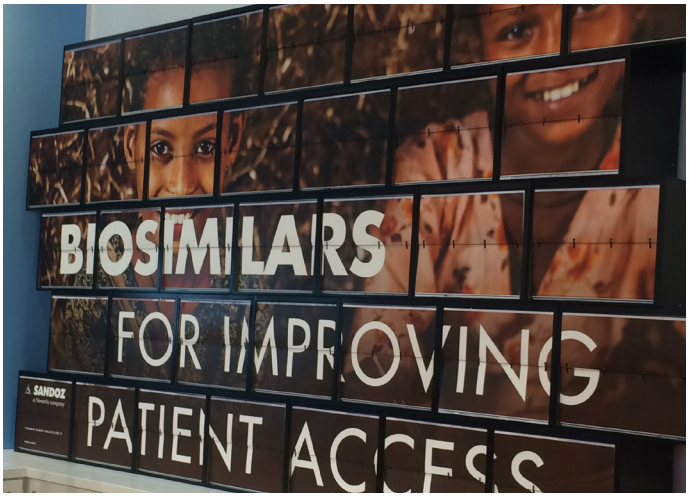
The results of a study conducted in Brazil have confirmed a relationship between personal exposure to fine pollution particles and lupus disease activity. "Our findings have shown that air pollution does not just increase the incidence and prevalence of chronic lung disease and acute respiratory infections, lung cancer, heart disease, and strokes, it is also an important contributory factor in childhood rheumatic disease, such as lupus," explained Ms Maria Fernanda Giacomin, Department of Paediatric Rheumatology, University of São Paulo, São Paulo, Brazil. "With air pollution increasing in many major cities, paediatric rheumatologists can expect to see a resultant impact on the disease activity of their lupus patients," she said.

The research found that there was a significant increase in lupus activity at 4 and 11 days after exposure to air with an increase of 18.12 $\mu g/m^3$ in the daily concentration of the PM2.5 pollutant. Two biomarkers were also measured following exposure to the air pollutant, demonstrating significant acidification of exhaled breath condensate at Days 7 and 10; an increase in exhaled nitric oxide was also found. The measurements taken from the biomarkers suggest a significant increase in airway inflammation related to air pollution, but there was no evidence that acute respiratory symptoms were increased.

It is estimated that there are nearly half a million premature deaths each year in the European Union as the result of air pollution. In busy cities with lower quality of air, the average life expectancy can drop by over 2 years. The World Health Organization (WHO) estimates one in eight of total deaths globally are also the result of air pollution exposure.

## Genetic Profiling Could Predict Ineffective Treatment Approaches for Arthritis Patients

GENETIC profiling could predict which treatments rheumatoid arthritis (RA) patients are likely to be responsive to, reducing the risks of damage caused by the disease, a EULAR press release, dated 9th June 2016 reports.





Genetic profiling is an approach which could provide clinical rheumatologists with valuable information to inform their management of RA, hopefully towards more personalised medicine. The use of tumour necrosis factor (TNF) inhibitor drugs can be an effective treatment of the inflammatory disease, but good disease control is reported in only 30% of patients. Prior knowledge of whether patients are unlikely to respond to certain anti-TNF drugs would allow alternative therapies to be prescribed, providing faster relief of symptoms and a reduced risk of future damage.

> “In current clinical practice, RA drugs are administered on a trial and error basis; there are no clinical biomarkers of response to guide treatment decisions.”

Mr James Oliver, Centre for Musculoskeletal Research, University of Manchester, Manchester, UK, said: “In current clinical practice, RA drugs are administered on a trial and error basis; there are no clinical biomarkers of response to guide treatment decisions. While non-responding patients can be switched to alternative therapies at 3 months, many remain on ineffective therapy for longer periods.” Mr Oliver concluded that blood-based biomarkers would support the timely switching of drugs for patients whose disease activity is not controlled by a particular drug, reducing the impact of long-term damage, and facilitating more responsible spending on RA drug treatment.


In research presented at EULAR 2016, early predictors of responses to treatment from blood samples were identified. A distinct pattern of changes was shown in the gene expression of RA patients who had a good response to a TNF inhibitor at 3 months, but not in non-responders. It also revealed that specific genetic marker allele*2 of the HS1,2A enhancer region influences response to therapy in the early stages of RA. These developments could be used to contribute to personalised therapy in RA.

## Nanotechnology Offers Effective Approach for Arthritis Diagnosis and Treatment

NANOPARTICLES could be used to enable rheumatologists to detect the early onset of rheumatoid arthritis (RA) and offer patients an efficient long-term approach to its treatment according to a EULAR press release dated 8th June 2016.

Biodegradable polymer nanoparticles (BNPs) coated in a peptide, which exclusively target inflamed joint tissue could be used to effectively deliver drugs and diagnostic probes into arthritis joints. Lead investigator Prof Paolo Macor, Department of Life Sciences, University of Trieste, Trieste, Italy, explained that due to diagnosis often being late in the development of RA, remission is uncommon, with many patients failing to respond to treatment. “There is therefore a need to develop a new tool to enable early diagnosis, and also to develop tissue-specific agents able to reduce systemic side effects. This would increase the potency of the drug with lower doses, and also potentially reduce the cost of treatment.”

> There is therefore a need to develop a new tool to enable early diagnosis, and also to develop tissue-specific agents able to reduce systemic side effects.

BNPs are unlike conventional treatments because they can be designed to deliver therapeutic agents directly to the site of inflammation. They can also be used as a diagnostic tool when filled with a contrasting agent such as gadolinium for early identification of joint inflammation. In previous research an injection of BNPs filled with methotrexate completely resolved inflammation in a rat model with antigen-induced arthritis. The same dose of free methotrexate into the bloodstream of the rat was found to be ineffective. A similar therapeutic effect was found using methotrexate-filled BNPs in a mouse model of chronic collagen-induced arthritis while the same dose of free methotrexate again proved unsuccessful.

"The advantage of being able to deliver methotrexate in this targeted way is to be able to gain the benefits from this key treatment of RA, while reducing the risk of adverse effects that are more frequent at high doses," Dr Macor added.

## Presence of Antibody in Arthritis Patients Could Inform Treatment Choice

CORRELATION between the presence of a specific antibody in patients with rheumatoid arthritis (RA) and responses to different drug treatments, discovered by a recent study, could improve early stages of treatment, a EULAR press release dated 9th June 2016 reports.


Researchers tested whether the presence of the anti-cyclic citrullinated peptide (anti-CPP) antibody, which causes more severe forms of RA, was predictive of patient responses to treatment. The team also assessed whether the rheumatoid factor antibody was a predictor. The results of their study showed that the presence of the anti-CPP antibody in RA patients was associated with a better response to the T cell co-stimulation blocker abatacept. The presence of the antibody was not correlated with the effectiveness of a tumour necrosis factor (TNF) inhibitor.

"These findings are exciting as anti-CCP antibodies are a marker of disease severity and detectable early in the course of disease. A better understanding of the relationship between anti-CPP antibodies and treatment response has the potential to advance patient care," Dr Leslie Harrold, Department of Orthopedics and Physical Rehabilitation, University of Massachusetts Medical School, Worcester, Massachusetts, USA, explained.

**More than 4,000 abstracts were submitted**

> These findings are exciting as anti-CCP antibodies are a marker of disease severity and detectable early in the course of disease. A better understanding of the relationship between anti-CPP antibodies and treatment response has the potential to advance patient care.

The study examined 566 RA patients who received the treatment abatacept and 1,715 patients who received a TNF inhibitor. Of those who received abatacept, both anti-CPP and rheumatoid factor antibodies were elevated in 244 patients and this group was associated with a significantly greater treatment response compared with those treated who had neither antibody (155 patients). The 167 patients with only a single marker elevated had a greater likelihood of remission as compared with those without either antibody. There were no significant differences found among the patients who received the TNF inhibitor regardless of which antibodies were present. The researchers suggested that the differential effect of the anti-CCP antibody on treatment response may be due to different mechanisms of actions between the treatments.


## Adolescents with Arthritis Susceptible to Depression

THE CHILDHOOD Arthritis Prospective Study has confirmed a link between the severity of depression and level of disease activity in adolescent patients suffering with juvenile inflammatory arthritis (JIA). The findings were presented at this year's EULAR congress in London, according to a press release dated 9th June 2016.

JIA is the most common paediatric rheumatic disease; it is hoped that these results will spur health services to provide a higher level of psychological support for young people with the disease. Lead author of the study Dr John Ioannou, Department of Medical Sciences, University College London, London, UK, discussed the lack of attention afforded to this sensitive age group: "We already know there is an association between depression and disease severity in rheumatoid arthritis [...] However, there has been much less work looking at depression in adolescents with JIA. Specifically, the association between depression and disease severity from initial assessment over a 48-month follow-up period has never been explored in this vulnerable age group with JIA."

The study consisted of a population of 102 adolescents who were within 6 months of the onset of JIA. Assessing participants with the Mood and Feelings Questionnaire, the team determined that one in seven of the patients suffered from significant symptoms of depression. This rate was frequently found to be more than double that of depression in the general adolescent population, when compared with data from previous studies.

> ...the association between depression and disease severity from initial assessment over a 48-month follow-up period has never been explored in this vulnerable age group with JIA.

Upon patients' first appraisal, those with more acute symptoms of depression demonstrated a significantly higher patient rating of disease severity, experiencing inflammation

and restricted movement of joints, pain, and disability to a greater extent than others. During the first 12 months of treatment, these symptoms reduced rapidly and then stabilised, causing a shift in the association between patients' depression and severity of the disease. Whilst depressive symptoms remained associated with future higher level of ongoing disability and pain, they were no longer associated with future inflamed joint count or patient rating of disease severity.

## Potential Treatment Alternative for Refractory Children with Autoimmune Disease

INHIBITORS of the tumour necrosis factor (TNF) protein could be an effective alternative for children with juvenile dermatomyositis (JDM) who have become refractory to multiple drug treatments.

TNF inhibitors were used to treat 66 patients with JDM in a study that resulted in significant improvements in muscle and skin involvement, as well as in overall disease activity. This rare chronic autoimmune disease affecting children is characterised by inflammation of the muscles, skin, and other organs. Its symptoms also include skin rash, skin ulceration, and muscle weakness. In the UK, JDM has a reported incidence of two to three cases per million in children <16 years old, with a median age of 6.8 years old at onset of the disease.



Some children with JDM experience multiple failed responses to different treatments. The resulting prolonged disease activity is associated with increased mortality and complications, including pain due to trapped nerves, scarring, and shortening of the muscles preventing joint extension. "High levels of the cell signalling protein TNF have [also] been reported in JDM patients with a long disease course, suggesting this immune cell regulator may play a significant role in refractory disease," explained Dr Raquel Campanilho-Marques, Clinical Research Fellow at the Institute of Child Health, University College London, London, UK.

> "High levels of the cell signalling protein TNF have [also] been reported in JDM patients with a long disease course, suggesting this immune cell regulator may play a significant role in refractory disease."

Changes in the level of muscle improvement in the patients were significant, measured according to the median value of both the Childhood Myositis Assessment Scale and Manual Muscle Testing, with $p<0.0001$ and $p=0.0097$, respectively. Improvements in skin involvement were measured using a modified skin Disease Activity Score with a significant difference from baseline ($p<0.0001$). Global disease activity improvement was measured and was also significantly improved ($p<0.0001$). Some of the participants (around one-quarter) discontinued their treatment with anti-TNF agents due to therapy failure, adverse events, or patient preference for subcutaneous administration.

## Awareness Raised of Sexual Disturbances Experienced by Arthritis Patients

RESEARCH presented in a EULAR press release dated 10th June 2016 has highlighted the importance of awareness of the sexual problems experienced by patients with rheumatoid arthritis (RA).

"Sexuality is an important dimension of an individual's personality, and sexual problems

can have a seriously detrimental impact on a couple's relationship," said Dr Pedro Santos-Moreno, Department of Rheumatology, Universidad La Sabana, Bogota, Colombia. "It is therefore rather surprising that up until now, very little quality research on sexual disturbances in RA patients has been published in the literature, bearing in mind how common the problems are," he explained.

The study assessed a population of 1,298 RA patients with an average age of 55 years and information was collected about their sexual activity through semi-structured interviews and non-probability sampling. The majority of the population (n=1,048) were women and 250 men made up the minority. More than a third of the participants reported a sexual disturbance.

Sexual activity was reported in 60% of women and 69% of men yet sexual disturbances were reported in 36% and 34%, respectively. These disturbances included dyspaereunia, orgasmic dysfunction, a lack of sexual desire, premature ejaculation, and a non-satisfactory sexual life. The relationship between having a sexual disturbance and RA disease activity was not found to be statistically significant.

The study explored different types of factors that were believed to influence the prevalence and severity of sexual disturbances in patients with RA. Precipitating factors reported in women and men included infidelity at 33% versus 6%; insecurity in a sexual capacity at 32% versus 16%; and biological or physical causes at 17% versus 3%, respectively. Factors thought to be responsible for the continuation of sexual disturbances included biological causes (women 11% versus men 15%); infidelity (women 9% versus men 4%); and depression or anxiety (women 1.9% versus men 5%). The relationship between these factors and disease activity was also not statistically significant.

> "Sexuality is an important dimension of an individual's personality, and sexual problems can have a seriously detrimental impact on a couple's relationship."

## Behavioural Interventions Motivate Arthritis Patients to Change Sedentary Lifestyle

MOTIVATIONAL text messages and personalised counselling have motivated rheumatoid arthritis (RA) patients to significantly reduce their sedentary behaviour and follow a healthier and more active lifestyle.

Individuals with the chronic disease tend to fail to meet the public health recommendations for daily moderate and vigorous physical activity in their respective countries. In Demark, 67% of patients do not meet the public health recommendations; similar rates were also found in Germany (68%) and the UK (67%). Patients with RA can find it difficult to maintain physically active lifestyles due to the pain experienced as a result of the disease.

A EULAR press release dated 10th June 2016 states that patients who self-reported a sitting time >5 hours and scored <2.5 in the Health Assessment Questionnaire took part in the study. They received three individual counselling sessions with a health professional over the duration of the study as well as regular text messages. The interventions were designed to improve motivation to reduce sitting time and increase physical activity.

The use of these behavioural interventions were found to be effective at reducing daily sitting time compared with matched

controls, with a between-group difference of 2.20 hours in favour of the RA intervention group (n=75 patients) compared with the control (n=75) group controls at 16-week follow-up. This is significant because RA patients tend to be more sedentary compared with the general population.

"We know that behavioural approaches are effective in reducing sedentary behaviour in healthy populations," Miss Tanja Thomsen, Center for Rheumatology and Spine Diseases, Rigshospitalet, Copenhagen, Denmark, explained. "Our findings support the introduction of behavioural approaches as an effective way to improve the health of rheumatoid arthritis patients, which may also be applicable in other populations with chronic disease and limited mobility," she said.

## Female Sex Hormone Offers Insight into Treatment of Systemic Sclerosis

THE SEX bias towards females that is present in systemic sclerosis (SSc) could lead researchers towards a new hormonal therapy approach for the difficult-to-treat condition, states a EULAR press release dated 10th June 2016. Affecting multiple organs, SSc is an autoimmune disease causing the excessive production of proteins such as collagen that results in skin thickening. It predominantly occurs in women with a reported female-to-male ratio of up to 9:1. Prof Jerome Avouac, Department of Rheumatology, Paris Descartes University, Paris, France, explained: "Because of the clear sex bias in SSc, we decided to assess if blocking the action of oestrogens (female hormones that decrease in menopause) plays a role in the development or vulnerability to this disease."

> "Because of the clear sex bias in SSc, we decided to assess if blocking the action of oestrogens (female hormones that decrease in menopause) plays a role in the development or vulnerability to this disease."

The research team first used mice to evaluate the effect of oestrogen inhibition in experimental models of skin fibrosis which represented the process of SSc. A population of mice whose key receptor to oestrogens had become unresponsive as a result of gene inactivation were examined. The researchers also used tamoxifen to block the action of oestrogen in another population. The results showed that inhibiting oestrogen was consistent in significantly worsening the process of skin fibrosis.

The second experiment conducted by the researchers involved stimulating the cytokine transforming growth factor β to activate skin fibrosis in SSc patients, followed by incubation with either different concentrations 17-β-oestradiol, the oestrogen inhibitor tamoxifen, or a combination of both. Measurements including the release of collagen from the fibroblasts and the differentiation of these fibroblasts into myofibroblasts confirmed that the oestrogen hormone significantly slowed down fibrosis. Although there is currently no proven effective treatment of SSc with an acceptable toxicity profile, the results of this study could lead to introducing the approach of hormone therapy as a treatment of SSc skin disease.

## Facebook Illuminates Diagnostic Delay for Inflammatory Back Pain

FAILURE to correctly diagnose the roughly 700,000 people living with inflammatory back pain (IBP) is a result of both poor GP awareness and lack of patient presentation, however social media can play a significant role in ameliorating this struggle, reports a EULAR press release dated 9th June 2016.

Although the vast majority of 17.3 million cases of back pain in the UK are related to mechanical causes, a significant number of these cases are in fact a result of inflammatory factors. IBP is characterised as persisting for >3 months, improving with exercise and not with rest, insidious in onset, and pain at night with morning stiffness. Early diagnosis relies on recognition of this mosaic of symptoms and can greatly improve patient mental health, ability to work, and quality of life.

Diagnosis can be delayed as much as >8 years, with one-third of diagnosed patients not referred to a rheumatologist.

Dr Arumugam Moorthy, Department of Rheumatology, University Hospitals of Leicester NHS trust, Leicester, UK, implored that: "Patients with IBP can wait years for a correct diagnosis. Early treatment is critical in achieving better outcomes for these patients." The development of tumour necrosis factor inhibitors and other biological therapies makes early treatment even more significant, as they improve functional ability and reduce inflammation in those unresponsive to standard drug therapy.

> "Patients with IBP can wait years for a correct diagnosis. Early treatment is critical in achieving better outcomes for these patients."

Comparing Facebook with other methods of advertising, 585 individuals were recruited to take part in online diagnostic surveys. The results of these recruitment methods were then analysed, providing a number of valuable insights. Mean ages were 41.5 years in the Facebook group compared with 59.1 years in the non-Facebook group; magnetic resonance were 45% and 45%, and X-ray imaging rates were 50% and 59%, respectively. "Although most (81%) of the chronic back pain patients we recruited through Facebook had consulted their GP, only 13% had actually been referred to a rheumatologist, confirming the need for additional GP education," explained Dr Moorthy.

## Early detection of Heart Problems in Systemic Sclerosis with Implant Device

EARLY detection of potentially fatal heart problems using a heart monitor implant could help save lives. The results of a pilot study were presented in a EULAR press release, dated the 9th June 2016. The findings suggest that potential fatalities from undetected heart problems could be significantly reduced by the insertion of a small device (similar in around the size of a pack of chewing gum) in patients with systemic sclerosis (SSc), an autoimmune disease which can put the heart at risk.


Dr Lesley-Anne Bissell, Research Fellow at the Faculty of Medicine and Health at the Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK, argued that this research is timely because cardiac problems have historically been difficult to detect, saying: "We know that cardiac involvement in SSc is associated with a very poor prognosis, accounting for between 14% and 55% of deaths with SSc."

The heart monitor, also known as an implantable loop recorder, is designed to store electrocardiographic data and can detect any significant changes in heart rhythm, or store data in response to patient activation when symptoms are experienced. Furthermore, the procedure is fairly simple, taking just 15–20 minutes, and is already a well-established practice in cardiology; the subcutaneous single-lead device is inserted through a small cut under the skin in the upper left chest under local anaesthetic. There are no wires as the electrodes that monitor the heart's activity are located on the surface and the device is covered by a protective case.

> "Early diagnosis and treatment to reduce the risk of complications is therefore essential and crucial for a positive outcome."

In this study, the device picked up a range of heart rhythm abnormalities in >50% of the 19 SSc patients, including supraventricular ectopics, ventricular ectopics, ventricular tachycardia, and complete heart block. Dr Bissell concluded: "Early diagnosis and treatment to reduce the risk of complications is therefore essential and crucial for a positive outcome."

## Association Between Juvenile Inflammatory Arthritis and Diabetes

SUSCEPTIBILITY to various autoimmune disorders has been found in patients with juvenile inflammatory arthritis (JIA). JIA is characterised by idiopathic chronic inflammation of synovial joints persisting for ≥6 weeks. This can happen to children as young as 1-year-old according to a EULAR press release on 9th June 2016. Recent research has suggested that JIA may be related to a number of genes that present risk factors for other autoimmune diseases. This means that children who suffer from JIA may also suffer from multiple autoimmune diseases.

A study based on the German national paediatric rheumatologic database looked at the association between JIA and diabetes. The study included 9,359 JIA patients with a mean age of 12 years. Within this cohort there were 50 children who had been diagnosed with diabetes in addition to JIA. When comparing this with a matched control group there was a significantly increased prevalence ratio: 1.92 for females and 2.04 for males.

"We know that there is a clear increase in the prevalence of JIA in young people with Type 1 diabetes compared with the general paediatric population," said Dr Kirsten Minden, Rheumatism Research Centre, Berlin, Germany. Further research found that 58% of the patients with both diseases had developed diabetes first, on average 5 years prior to developing JIA. Those who had JIA first typically developed diabetes 3 years later.


Dr Minden suggests that the study has allowed for some positive steps to be taken, concluding that "[however] this study shows the reverse correlation that Type 1 diabetes occurs more commonly in patients with JIA. The next step is to explore in detail the factors and mechanisms that link the two diseases, and confirm that these findings are applicable to other geographic areas, where different environmental and genetic factors are at play. By better understanding this link, we may be able to develop new preventative and therapeutic interventions."

## Biosimilar Switching may not Solve Problems

NOVEL research suggests that patients who generate an immune response to infliximab should not be switched to the biosimilar due to a cross-reaction from developed antibodies, according to a EULAR press release dated 8th June 2016.

Researchers have found that antibodies responding to infliximab will also react similarly to the first biosimilar to be introduced and approved in Europe. Infliximab is a tumour necrosis factor inhibitor, that is used to treat various inflammatory rheumatic diseases including rheumatoid arthritis and ankylosing spondylitis. Patients who develop antibodies responding to the biopharmaceutical can experience a limited clinical efficacy and reduced safety profile, requiring alternative treatment as a result. However, switching to the use of its biosimilar may continue to expose the patient to these risks.

In a recent study, infliximab was administered to 250 rheumatoid arthritis and spondyloarthritis patients who had not previously received treatment with the biosimilar. Following this, the team assessed the concentrations of anti-infliximab antibodies using assays. Half of the patients (50.4%) treated tested positive for the antibodies and every one of the patients in this category also exhibited antibody reactivity against the biosimilar.

"Our results have shown that all the antibodies that developed in patients being treated [with Infliximab] cross-reacted with the biosimilar. The presence of these anti-infliximab antibodies is likely to enhance clearance of

the drug from the body, potentially leading to a loss of response, as well as increasing the risks of side effects," Dr Daniel Nagore, Research and Development Director of Protein Research, Progenika Biopharma, Derio, Spain, explained.

## Repetitive Prolonged Physical Workloads Increases Rheumatoid Arthritis Risk

REPETITIVE prolonged physical workloads (RPPW) have for the first time been shown to increase the risk of developing rheumatoid arthritis (RA), according to research presented at EULAR 2016. Prolonged work-related activity over many years is known to cause many cases of osteoarthritis, but this study is the first to associate specific patterns of physical workload with RA. This was achieved through analysis of different types of self-reported RPPW exposures from a population of 3,680 patients with RA and 5,935 matched controls included in the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA).

> "We found that some types of physical workload increased the odds of developing RA more than others."

To determine whether some people could be considered more susceptible than others, the risk factor for developing RA was compared between individuals with and without the genotype *HLA-DRB1*, along with an analysis addressing the presence or absence of anti-citrullinated protein antibodies among those with disease.

"We found that some types of physical workload increased the odds of developing RA more than others," Miss Pingling Zeng, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden, explained in a EULAR press release dated 10th June 2016. "There also appeared to be a significant interaction between genetic makeup, in terms of *HLA-DRB1* genes, and the risk of ACPA-positive RA from specific types of physical workload," she added.

The estimated odds ratio in exposed versus unexposed participants was ≥1.5. Exposure to seven different types of RPPW and the risk of RA was investigated: exposure to vibration carried a ratio of 1.5; carrying or lifting weights >10 kg was 1.5; bending and turning was 1.6; working with hands below knee level was 1.7; and working with hands above shoulder level was 1.8. "These new insights into the cause of RA may hopefully lead to effective strategies to prevent the development of RA, particularly in those RA patients with a susceptible genotype," Ms Zeng said.

## Researchers Point to the Significant Role of Patient Perspectives in Arthritis Treatment

THE IMPORTANCE of patient perspectives has been highlighted in research presented at EULAR 2016 in a EULAR press release dated 8th June 2016, which revealed the prevalence of anxiety among patients towards their treatment and care.

A patient-survey with 3,649 respondents made up of patients with rheumatoid arthritis (RA) revealed common concerns and desires regarding treatment. It showed that the majority (62%) of patients felt uncomfortable raising concerns about treatment and their disease to their healthcare provider (HCP). Of the patients seeing a HCP, 34% felt that asking too many questions would result in them being perceived as a difficult patient and could affect the quality of care.

Out of the 2,139 RA patients receiving medication, more than half were worried their medications would fail (57%) and desired more choices in medication (56%). "Further understanding the responses from this survey will be important to facilitate communication between patients and HCPs, with the ultimate aim of improving treatment outcomes," explained Ms Cheryl Koehn, President of Arthritis Consumer Experts, Vancouver, Canada.


Other research presented at EULAR 2016 demonstrated that RA patients and their HCPs highly value patient participation in multidisciplinary team conferences. In follow-up interviews with five HCPs and eight patients who had attended their first conference, researchers explained that the patients felt they were taken seriously, treatment goals were set in mutual agreement, and the resulting medical approaches were clear and satisfactory.

Researchers demonstrated how expert patients, known as Patient Partners® who train medical professionals on the clinical presentation of RA, have updated their teaching to incorporate the role of patient perspectives. As a result, four new course modules were implemented covering aspects of treatment delay, perceptions about medication, the patient and their environment, and active participation.

## Unhealthy Lifestyle Choices of Arthritis Patients Significantly Reduce Likelihood of Remission

SMOKING and obesity significantly reduce the likelihood of remission for patients with rheumatoid arthritis (RA) in the early years of the disease, a EULAR press release dated 9th June 2016 reports.

The researchers of a recent study explained that despite a high prevalence of excess body weight and smoking among RA patients, little is known about the extent to which these lifestyle factors impact the probability of a patient achieving sustained remission. Many patients fail to achieve or maintain remission and at least half of individuals with RA in developed countries are unable to maintain a full-time job within 10 years of the onset of the disease. Dr Susan Bartlett, Associate Professor at the Medicine Faculty, McGill University, Montréal, Québec, Canada, explained: "Our findings show that not smoking and a healthy body weight (lifestyle factors, which can be modified by patients) can have a significant impact on becoming symptom free."

The study examined 1,008 patients diagnosed with RA, 72% of whom were female. Among males, 131 (47%) were overweight, 93 (33%) obese, and 55 (20%) smoked. Among females, 220 (30%) were overweight, 241 (33%) obese, and 109 (15%) smoked. Following adjustment for other factors such as age, race, and experience with methotrexate, smoking and excess weight were shown to have significant independent and combined effects on the likelihood of achieving sustained remission in both men and women within the first 3 years of diagnosis. The findings also showed that males were more likely to achieve remission than females.

Dr Bartlett spoke passionately of the need to advise patients saying: "If you have a history of RA in your family and you smoke you are pouring gasoline on the situation," also stating that: "If you are obese you are half as likely to achieve sustained remission in RA." These conclusions suggest that encouraging patients and advising them of the dangers of these lifestyle factors is essential.

## New Tool Predicts Impact of Comorbidities in Psoriatic Arthritis

EVALUATING the risk of hospitalisation and premature death in patients of psoriatic arthritis (PsA) with associated comorbidities may soon be possible thanks to a new method developed in a recent study, according to a EULAR press release dated 9th June 2016. Researchers were able to construct a model to prospectively assess patients who are most at risk. It is hoped that more accurate predictions of these outcomes could improve healthcare costs, use of resources, and outcomes for patients.

Dr Yasser El Miedany, Department of Rheumatology, Darent Valley Hospital, Dartford, UK, commented: "To date, no disease-specific models had been developed to identify those comorbidities with the greatest impact on PsA patients' health status. We have now developed and validated a PsA comorbidity index (PsACI), which will enable clinicians to prospectively include comorbidities assessment and management in their standard practice."

The study examined 1,707 patients over a 10-year period in a retrospective, multicentre analysis. A morbidity index score was calculated using different cut-off values to identify patients at certain stages of risk for hospitalisation and death. The researchers found a higher incidence of comorbidities and higher risk of hospitalisation in men who were older in age at the time of disease onset and who had a high BMI at baseline ($p<0.05$). The team were also able to identify that cardiovascular disorders, osteoporosis, falls, depression or anxiety, diabetes mellitus, renal and liver diseases, lung and gastrointestinal problems, and infection were the comorbidities most strongly associated with a 10-year risk of hospitalisation or death ($p<0.001$).

Alongside these conditions, a Multidimensional Disease Severity score (based on Disease Activity Index for Psoriatic Arthritis, Psoriasis Area and Severity Index, enthesitis, erythrocyte sedimentation rate, and C-reactive protein) was another significant independent indicator of disease outcome at 10 years. The PsACI, when adjusted for a number of patient variables, showed scores from 0–36, with 14.5 being the cut-off point associated with a sensitivity of 97.5% and specificity of 87%.

## Positive Attitude Linked to Treatment Adherence in Arthritis

NEW insights into why patients with rheumatoid arthritis (RA) do not adhere to their therapy even in its early stages could be used to optimise outcomes of the disease according to the results of two recent studies, a EULAR press release dated the 10th of June has stated. Non-adherence to the treatment of RA has been shown to be a serious problem affecting disease activity, according to Prof Johanna Hazes, Head of Rheumatology, Erasmus University Medical Center, Rotterdam, Netherlands. "However, it remains unknown as to why so many RA patients do not adhere to their treatment," she added.

Prof Hazes sought to identify which inflammatory arthritis patients were at risk of failing to adhere to treatment within the first 3 months. The research assessed 259 adults recently diagnosed with inflammatory arthritis who were receiving disease-modifying anti-rheumatic drugs (DMARDs). Each participant was interviewed to identify potential adherence predictors and electronically monitored pill bottles were used to continuously monitor their commitment to treatment using electronic pill bottles.

Adherence was found to decline rapidly over the first 3 months despite an initially high uptake in treatment. The researchers found that out of 15 different potential predictors of adherence, the factors 'information seeking' and 'having positive expectations about their disease' identified in patients had a significant association with sticking to the course of treatment. Patients who identified as 'adjusting to the pain' were associated with non-adherence.

Methotrexate is often the first step of drug treatment for RA but it has a highly variable response rate. Research into the potential predictors of response to methotrexate found that participant anxiety on starting treatment was a predictor of non-response, likely as the result of its negative effect on adherence. This finding is hoped to facilitate a faster prescription of alternative drugs to the right patients and a reduction in disease progression.

## Risk of Late Onset Rheumatic Disease Reduced by Childhood Appendicitis

CHILDHOOD appendicitis dramatically reduces the risk of ankylosing spondylitis (AS) later in life, findings which could help explain how the inflammatory disease develops according to a EULAR press release dated 10th June 2016. AS is a progressive form of arthritis which is caused by chronic inflammation of the joints in the spine and other parts of the body. In Europe, the prevalence of AS is estimated at 23.8 cases per 10,000 people. In comparison, North America has a prevalence of 31.9 cases per 10,000 people. AS is strongly associated with the genotype *HLA-B27*, however positive testing for the marker in a person does not guarantee they will develop the disease.

> "One potential explanation is that inflammatory responses elicited during the course of childhood appendicitis somehow induce long-lasting immunological changes in the colonic mucosa, which in turn protect these individuals from developing AS."

A recent study examined 2,642 patients with AS and 11,064 matched controls, and found that childhood appendicitis reduced the odds of a diagnosis of AS later in life by 40%. It also found that hospitalisation due to a childhood respiratory tract infection increased the odds by 20%. Mr Ulf Lindström, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, explained that: "Despite decades of effort to understand its aetiology, the causes of AS remain poorly characterised, so this is a significant development in helping us better understand this debilitating disease."

"Appendicitis has previously and repeatedly been shown to decrease the risk of developing ulcerative colitis, but up until now had not been investigated for AS," explained Mr Lindström. The occurrence of appendicitis and its effect on intestinal disorders such as ulcerative colitis could have a significant impact on preventing the development of AS. "One potential explanation is that inflammatory responses elicited during the course of childhood appendicitis somehow induce long-lasting immunological changes in the colonic mucosa, which in turn protect these individuals from developing AS," he said.

## Discordance in Perceptions of Osteoarthritis Severity Between Rheumatologists and Patients

VARIATION in perceptions of disease severity between patients and physicians can have negative impacts on treatment. This is according to researchers who have revealed that patients with osteoarthritis (OA) are more likely to have the impact of their condition underestimated by rheumatologists than patients with rheumatoid arthritis (RA).

"This discordance between physician and patient perception of disease severity is important because of the negative impact it can have on shared decisions concerning the best choice of therapy," the lead author of the study, Dr Isabel Castrejón, Department of Rheumatology, Rush University Medical Center, Chicago, Illinois, USA, stated, "this in turn is likely to interfere with treatment compliance and future outcomes."

In the new study reported in a EULAR press release dated the 8th June 2016, the discordance of 243 OA patients and 216 RA patient's clinical status estimates with physician estimates was analysed. The results showed that 34% (82) of patients with OA perceived a greater disease severity than physician assessment, as did 18% (39) of RA patients. Physician evaluation of severity was greater than 15% (33) of patients with RA and 10% (25) of patients with OA. Patient and

physician evaluation of the disease was evaluated using a 0–10 visual analogue scale. Patient assessment also included completion of a multidimensional health assessment questionnaire which scored physical function, pain, and fatigue and involved a self-reported count of joints affected and a symptom checklist.

Previous studies have shown a variability of perceptions between physicians and patients in the impact of many different rheumatic diseases. Recent evidence suggests the disease burden in both OA and RA is similar but OA generally remains perceived as less severe than RA.

## Patient Welfare Above Cost in Treatment Decisions for Rheumatoid Arthritis

EVALUATION of therapeutic strategies utilised by consultant rheumatologists in the UK has found that cost is rarely a factor influencing their choice of tumour necrosis factor (TNF) inhibitor drugs prescribed for patients with rheumatoid arthritis, despite the recommendations of national guidelines.

The clinical guidance produced by the National Institute for Health and Care Excellence (NICE) recommends that rheumatoid arthritis patients in England should be treated with the lowest cost anti-TNF treatment. The findings of a recent study, outlined in a EULAR press release dated 10th June 2016, suggest that a range of other factors besides cost in fact influence treatment choice.

"Emergence of evidence, interpretation of clinical guidelines, patient involvement in decision-making, desire for clinical autonomy, and the involvement of clinical service commissioners have all been identified as influence factors. We now need further research to explore whether these deviations from NICE guidance lead to differences in patient outcomes, or cost-effectiveness of care," stipulated lead author of the study Mr Sean Gavan, Manchester Centre for Health Economics, University of Manchester, Manchester, UK.

In discussing the influences on key treatment decisions, consultants explained that cost was rarely a factor guiding their choice of first-line anti-TNF drugs, unless local service commissioners had imposed the use of the least expensive treatment. If the imposition had been made it was perceived to have sacrificed the involvement of patients in the decision-making process.

Careful manipulation of the Disease Activity Score 28 (DAS28), measuring the severity of rheumatoid arthritis, was cited by many of the consultants as a way to ensure clinical autonomy and freedom to prescribe patients clinically appropriate anti-TNF treatment, despite failure to meet a NICE threshold due to insufficient disease activity. The successful negotiation of local exceptions to NICE guidance through individual funding requests also caused considerations of cost to be overlooked when deciding on treatment options.


# INTRODUCING NEW BIOSIMILARS INTO CURRENT TREATMENT ALGORITHMS

## Summary of a Biogen-sponsored symposium, held at the European League Against Rheumatism (EULAR) Congress 2016 in London, UK, on 9th June 2016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## MEETING SUMMARY

Three biosimilar products are now licensed for the treatment of rheumatic diseases in Europe. The European Medicines Agency (EMA) requires that similarity between a biosimilar and its reference product is demonstrated using a rigorous, stepwise process that includes extensive physicochemical and biological analytical testing, non-clinical pharmacology, clinical evaluations, and pharmacovigilance plans. Each step is highly sensitive to any differences between products and progressively reduces any uncertainty over similarity; all steps must be satisfied to demonstrate biosimilarity. The US Food and Drug Administration (FDA) requires a similar stringent biosimilar development process.

The etanercept biosimilar SB4 (Benepali®), recently approved for the treatment of rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis (ankylosing spondylitis, non-radiographic axial spondyloarthritis), and plaque psoriasis, is herein used to demonstrate the detailed analytical characterisation and clinical testing that are required by the EMA before biosimilars are approved for use. A comprehensive characterisation study involving >55 physiochemical and >25 biological assays demonstrated that SB4 has highly similar structural, physicochemical, and biological quality attributes to reference etanercept. A Phase I study demonstrated pharmacokinetic equivalence between SB4 and reference etanercept in healthy male subjects. Furthermore, a Phase III, randomised, controlled trial performed in patients with

moderate-to-severe rheumatoid arthritis despite treatment with methotrexate (MTX) showed that SB4 was equivalent to etanercept in terms of efficacy, safety, and immunogenicity.

In conclusion, the biosimilar development process performed according to EMA or FDA guidelines is highly rigorous and comprehensive. Biosimilars such as SB4 are now available in clinical practice and are likely to improve access, reduce costs, and ultimately, improve health outcomes.

## INTRODUCTION

A biosimilar is defined by the EMA as "a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product."[1] In developing a biosimilar, the aim is to create a highly similar product with no clinically meaningful differences from the reference biological in terms of safety, purity, and potency. Three biosimilar products are now licensed for the treatment of rheumatologic diseases in Europe: two infliximab biosimilars (CT-P13 and SB2) and one etanercept biosimilar (SB4). Biosimilars have considerable potential to offer cost savings and increased accessibility to effective biologic disease-modifying anti-rheumatic drugs (bDMARDs).[2] However, it is crucial that clinicians are confident that biosimilars have no meaningful differences compared with their reference products.

The comprehensive and stepwise assessment of the totality of evidence required by the EMA for biosimilar development was reviewed by international experts at a Biogen-sponsored, interactive symposium held during EULAR 2016, and illustrated through the example of the recently-approved etanercept biosimilar, SB4 (Benepali®). Furthermore, the expert faculty and audience discussed the practical benefits of introducing these new biosimilars into treatment algorithms for rheumatic diseases.

## BIOSIMILARITY: AN INNOVATIVE REGULATORY AND DEVELOPMENT CONCEPT

Biological drugs are intrinsically complex proteins produced by living cells, and are highly sensitive to changes in manufacturing processes and storage conditions.[3] This complexity means that biosimilars cannot be generic or identical copies of the innovator biological because they are not created using exactly the same manufacturing conditions as the reference product. Thus, development of biosimilar products requires a rigorous and comprehensive set of comparability exercises and regulatory evaluation. According to the EMA, it needs to be demonstrated that the biosimilar is highly similar to its biological reference product, with no clinically meaningful differences in quality characteristics, biological activity, safety, and efficacy.[1] The active substance, posology, and route of administration for the biosimilar also need to be the same as for its reference product. Changes intended to improve efficacy are not considered part of the biosimilar approach.

*"You can't apply the generic rules, because they [biosimilars] are not generics. You cannot make a generic biosimilar."* (John D. Isaacs)

It is important to understand that currently used reference biologicals can themselves be considered as different versions of the original products at launch.[4,5] Because of the complexity of the products and their reliance on cell culture for production, it is impossible for any manufacturer to keep a biological perfectly consistent over time or across multiple production plants. Furthermore, the reference product may have undergone a number of intentional manufacturing changes since its approval. For example, reference etanercept (Enbrel®*) has undergone more than 20 post-approval changes.[4] Regulatory authorities have extensive experience in scrutinising and approving any such changes, with comparability exercises required when any critical changes are made to the manufacturing process, such as introducing a new purification step or setting up a new manufacturing site.

*"We are fortunate in Europe that the EMA has long experience in their consideration of biosimilars… this is why many clinicians have a lot of trust in what the EMA is actually doing in their regulatory pathways."* (Tore K. Kvien)

The EMA has pioneered the biosimilars development pathway (Figure 1), developing guidelines in 2005 and 2006 for approval of biosimilars using an abbreviated registration process. Of particular relevance to rheumatologists are the specific guidelines for monoclonal

antibodies, published in 2012,[6] and the guidelines for biotechnology-derived proteins, revised in 2015.[7] The World Health Organization (WHO), FDA, and regulatory authorities in Canada and Japan have produced similar guidance, as recently summarised.[2] In the European Union (EU), the EMA website provides a helpful overview of currently licensed biosimilars (www.ema.europa.eu)**. Biosimilars developed in countries with less rigorous regulatory pathways for such products are referred to as 'biocopies' or 'biomimics' and cannot necessarily be expected to have the same efficacy and safety profile as the reference biological.[8] Furthermore, biocopies may not be subject to rigorous pharmacovigilance processes to identify safety issues.

*"We have to be very careful that we do not compare what is happening in countries with regulatory EMA and FDA pathways with other countries that do not scrutinise their products so carefully."* (Arnold Vulto)

## STEPWISE ASSESSMENT FOR TOTALITY OF EVIDENCE REQUIRED TO ESTABLISH BIOSIMILARITY

One of the goals of biosimilar development is to establish biosimilarity, not to re-establish benefit and safety.[1] Biosimilarity is demonstrated using a rigorous stepwise process to generate a totality of evidence that incorporates results from extensive physicochemical and biological analytical testing, non-clinical pharmacology, and clinical evaluations (Figure 2). All steps must be satisfied to confirm biosimilarity i.e. eventual differences have no relevance for clinical efficacy and safety.

*"For the regular physician treating patients, it is sufficient to understand that EMA…are doing a comprehensive comparability exercise to look at analytical and in vitro data…Some of the details are very complex for regular clinicians, but this should not be a barrier to using these drugs."* (Tore K. Kvien)

In the EU, this stepwise assessment is a comprehensive and transparent process with the assessment history for each product documented in detail in the European Public Assessment Report (EPAR), published by the EMA. At present, this detailed information is not fully documented in the product's Summary of Product Characteristics (SmPC), which is, instead, identical to the reference product SmPC. It has been argued that, as the SmPC is the primary source of information for the physician, it should contain all pertinent information on the biosimilar as well as the reference product.[10,11]

*"The EMA is working on a third document… describing a summary of the EPAR for clinicians."* (Arnold Vulto)

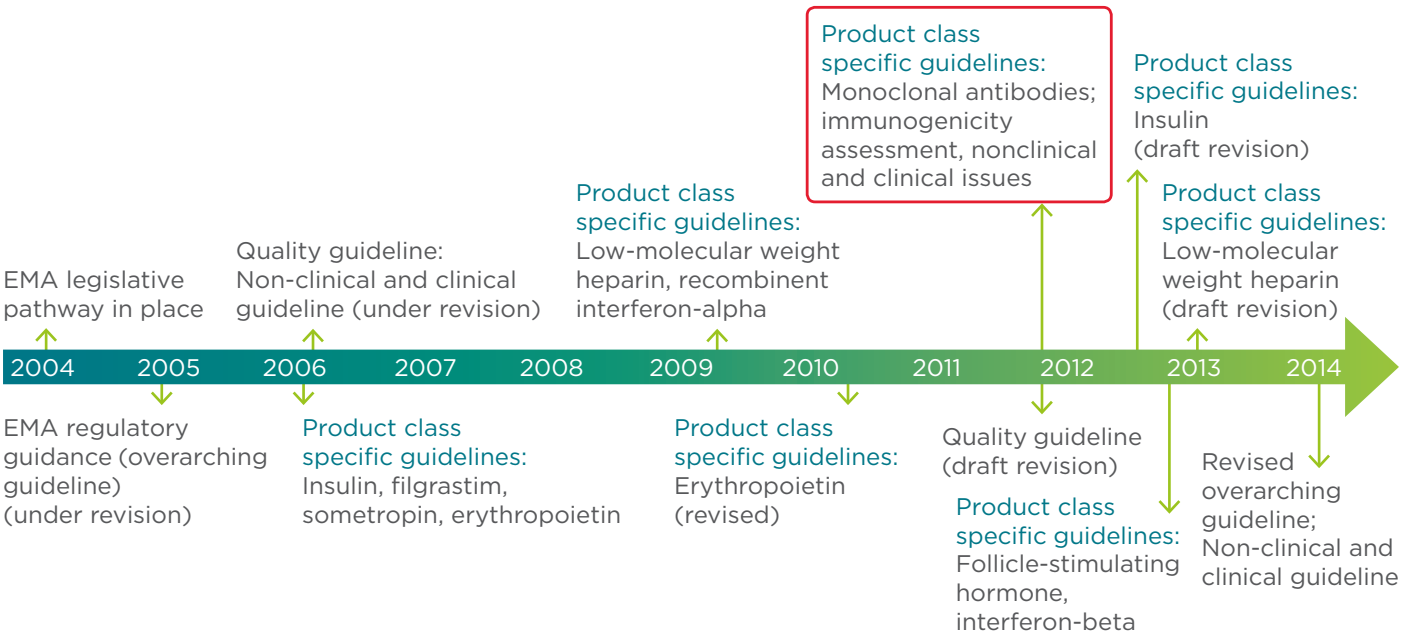


**Figure 1: The European Medicines Agency (EMA) pioneered the biosimilars development pathway: timeline of guidelines issued by the EMA to guide the development of biosimilars.**

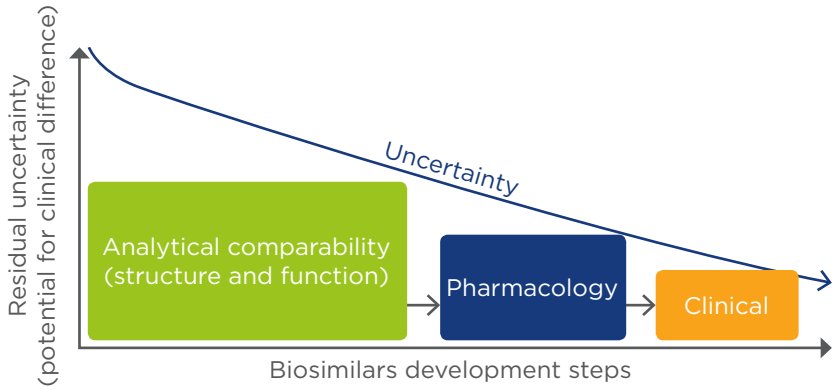


**Figure 2: Stepwise assessment for the totality of evidence required to demonstrate biosimilarity.[9]**

## Analytical Comparability

The biosimilar development process places significant emphasis on analytical methods to exclude any relevant differences between the biosimilar and its reference biological. A biosimilar should be highly similar to the reference product in physicochemical and biological terms, with any observed differences justified in terms of their potential impact on safety and efficacy.[1] Natural and manufacturing variability means that biologicals often comprise a mixture of protein isoforms, with differences in higher order structure, post-translational modifications (such as glycosylation), and charge profile.[12] This may result in changes in biological activity including receptor binding, effector function, cytotoxicity, and signal transduction. Characterisation studies are required that are "sensitive, specific, and sufficiently discriminatory to provide evidence that observed differences in quality attributes are not clinically relevant."[7] The EMA notes that it is not expected that all quality attributes will be identical and minor differences may be acceptable, if appropriately justified.[7] However, it is most important that attributes which are critical to the efficacy and safety of a drug (referred to as critical quality attributes [CQAs]) are identified and maintained across products.[7]

*"The rule for generic drugs is based only upon pharmacokinetic equivalence. Here we go far beyond that."* (Arnold Vulto)

SB4 (Benepali®) is an etanercept biosimilar that has been developed by Samsung Bioepis Co., Ltd. (South Korea), a joint venture between Samsung BioLogics and Biogen. SB4 is the first etanercept biosimilar approved for use in the EU and is manufactured in Denmark. The analytical comparability of SB4 and reference etanercept was established in accordance with the International Conference of Harmonization comparability guideline[13] and the biosimilar guidelines of the EMA and FDA. Characterisation studies included >55 physiochemical tests and >25 biological assays to provide an extensive comparison of primary, secondary, and tertiary structure, purity and process-related impurities, glycan content and identity, and biological activities based on the mechanism of action.[14] These studies used sophisticated, state-of-the-art assays and are considered more sensitive than clinical measures at detecting small differences between molecules as they inherently exclude heterogeneous patient or disease factors. This comprehensive characterisation exercise clearly demonstrated that SB4 has highly similar structural, physicochemical, and biological quality attributes to reference etanercept.

*"Altogether, there were 80 tests described in detail [for SB4]…these data have been submitted to EMA and have been scrutinised."* (Arnold Vulto)

## Clinical Pharmacology

Regulatory agencies typically require a Phase I pharmacokinetic comparability study of a biosimilar and its reference product as the first step in a biosimilar clinical development programme. While pharmacokinetic equivalence is necessary to demonstrate biosimilarity, it is insufficient of itself and must be coupled with analytic comparability and a Phase III clinical study. Generally, a single-dose, crossover study with full pharmacokinetic characterisation in a homogeneous population is recommended to demonstrate biosimilarity.[7]

To show pharmacokinetic equivalence, the confidence intervals (CIs) of the test-to-reference ratios of relevant pharmacokinetic parameters must be contained within a pre-specified equivalence margin, agreed upon with the regulatory agency.[7]

In the SB4 Phase I study, 138 healthy males were randomised to receive a single dose of SB4, reference etanercept sourced in the EU, or reference etanercept sourced in the US during Period 1, followed by crossover treatment in Period 2.[15] The crossover design allowed each subject to receive two treatments, so that a comparison between the two treatments could be made with each subject acting as their own control. The comparison between the EU- and US-sourced products also provided scientific justification for the use of EU-sourced etanercept as the only active comparator in the Phase III study.

The mean serum concentration-time profiles were superimposable between the SB4 and reference etanercept sourced in the EU, SB4 and reference etanercept sourced in the US, and reference etanercept sourced in the EU and US. The geometric least squares means ratios of $AUC_{inf}$ (area under the concentration-time curve to infinity), $AUC_{last}$ (AUC to the last quantifiable concentration) and $C_{max}$ (maximum concentration) were close to 1 for all comparisons, and the corresponding 90% CIs were completely contained within the pre-specified equivalence margin of 80–125%.

*"The study definitely met its expectations, showing that there were no pharmacokinetic differences between the biosimilar etanercept SB4 and the originator products."* (Tore K. Kvien)

The incidence of treatment-emergent adverse events (TEAE) was similar between treatments, with no serious adverse events or deaths reported during the study. It is recognised that differences in impurities and/or breakdown products between biosimilars and their reference products can affect immunogenicity. Antidrug antibodies (ADAs) can limit drug bioavailability and shorten half-life through the formation of immune complexes that accelerate drug clearance and/or impair binding. In this Phase I study, immunogenicity was evaluated pre-dose and at Day 29 after the first treatment. While the incidence of ADAs was lower after SB4 exposure compared with reference etanercept exposure, the EMA did not consider this numerical imbalance clinically relevant and did not preclude biosimilarity.[16]

## Clinical Assessment

Phase III, randomised, controlled trials designed to demonstrate equivalent efficacy and comparable safety, are the third step in removing uncertainty around the comparability of a biosimilar and its reference product. The EMA requires the trial to be performed in a sensitive population of patients with a disease for which the reference product is licensed and an equivalence margin should be pre-defined for the primary endpoint (American College of Rheumatology 20% [ACR20] response rate) based on the placebo-adjusted efficacy outcome derived from a meta-analysis of prior randomised controlled trials of the reference product.[1] Safety, including immunogenicity, should also be evaluated.

The clinical efficacy and safety of SB4 was compared with the reference product etanercept in a Phase III, multicentre, randomised, double-blind, parallel-group study performed in patients with moderate-to-severe rheumatoid arthritis despite treatment with MTX.[17,18] Patients receiving background MTX 10–25 mg/week were randomised to SB4 (n=299) or etanercept (n=297) administered as a weekly subcutaneous injection of 50 mg for 52 weeks. At the end of the double-blind treatment period, patients originally randomised to SB4 could continue in this treatment arm, while patients who were originally randomised to reference etanercept could be transitioned to SB4.[19] Only the EU-sourced version of reference etanercept was used in this study, which was considered acceptable as it had shown pharmacokinetic equivalence with the US-sourced version in the Phase I study.[15] The primary endpoint of the study was the ACR20 response rate at Week 24 in the per-protocol set. Although ACR20 is from a treatment perspective less relevant, it is established as the most sensitive endpoint to illicit any differences between the reference product and the biosimilar.

*"You have a sensitive population, you have a sensitive primary endpoint, and you select the per-protocol population to increase the opportunity to find a difference."* (Tore K. Kvien)

ACR20 response rates were 78.1% with SB4 and 80.3% with reference etanercept in the per-protocol set (Figure 3). The 95% CIs for the adjusted difference in ACR20 response rate

fell within the pre-specified equivalence margin of ±15% in both the per-protocol set (95% CI: -9.41 to 4.98%) and the full analysis set (95% CI: -5.24 to 9.07%), indicating therapeutic equivalence between products.[17] This equivalence was maintained over time, with the 95% CIs of the adjusted difference in ACR20 response rate at Week 52 also well-contained within ±15% in both the per-protocol set and full analysis set. Furthermore, the time-response curves of SB4 and etanercept in the full analysis set showed that ACR20, 50, and 70 response rates mirrored each other over the 52 weeks of the double-blind phase of the study.[18]

*"It is reassuring that the response curves… before they plateau beyond Week 16–24, they are quite comparable…and maintain the effect up to Week 52."* (Thomas Dörner)

Beyond clinical outcome measures, the modified Total Sharp Score was assessed at Week 52 in both groups.[18] The mean change from baseline in modified Total Sharp Score was comparable between the two treatment groups (0.45 for SB4 and 0.74 for reference etanercept).

The overall safety profile between SB4 and reference etanercept was comparable at Week 52.[18] There were minimal differences between SB4 and reference etanercept in terms of incidence of TEAEs (58.5% versus 60.3%, respectively), serious adverse events (6.0% versus 5.1%, respectively), TEAEs leading to study discontinuation (5.4% versus 6.7%, respectively), or serious infections (0.3% versus 1.7%, respectively). Injection-site reactions, grouped under the high-level term 'Administration-site reactions', occurred in fewer patients in the SB4 group at 52 weeks (3.7%) than the etanercept group (17.5%). The EMA concluded that this difference could have been at least partly due to an extensive split in the way that such reactions were reported and considered this numerical imbalance between the two arms of no clinical significance.[16] Malignancies were reported in four (1.3%) patients in the SB4 group (gastric adenocarcinoma, basal cell carcinoma, breast cancer, and metastatic lung cancer) and in one (0.3%) patient in the reference etanercept group (invasive ductal breast carcinoma). Two deaths were reported in the SB4 group, neither of which were considered related to treatment.

In the SB4 Phase III study, the incidence of ADAs at Week 24 was significantly lower in the SB4 group (0.7%) compared with the reference etanercept group (13.1%; p<0.001).[17] Only one sample from the reference etanercept group had neutralising capacity. The ADAs appeared early (between Week 2 and Week 8), and had mostly disappeared after Week 12. In a re-analysis excluding samples at Weeks 4 and 8, the overall ADA status at Weeks 24 and 52 was comparable and subgroup analyses by ADA status showed no apparent correlation between ADAs and clinical response or safety.[16] The evidence from this clinical trial confirmed the analytical and pharmacological data showing biosimilarity between SB4 and reference etanercept.

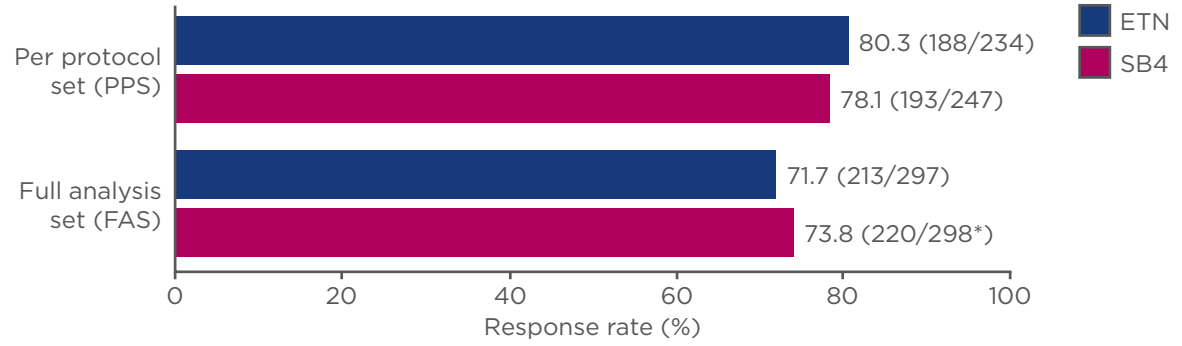


**Figure 3: American College of Rheumatology response rates (ACR20) at Week 24 in patients treated with SB4 or reference etanercept.**

PPS Adjusted difference: -2.22 (95% CI: -9.41 to 4.98), FAS Adjusted difference: 1.92 (95% CI: -5.24 to 9.07), [Predefined equivalence margin: -15 to 15%]

*One patient was excluded from the FAS due to missing efficacy data at baseline.

CI: confidence interval; PPS: per protocol set; FAS: full analysis set; ETN: reference etanercept.

*Modified from Emery P et al.*[17]

## PHARMACOVIGILANCE

As with all pharmaceuticals, rare adverse events may occur in clinical practice that were not detected during clinical trials. Therefore, careful post-marketing pharmacovigilance is important for both biosimilars and reference products. The EMA requires a risk management plan for all biologicals, including biosimilars, and states that all appropriate measures should be taken to clearly identify any biological medicinal product which is the subject of a suspected adverse event report.[7]

*"It is critical in terms of pharmacovigilance…that you as the clinician know what drug your patient gets…including the batch number…if there is a problem, we should be able to trace it back to which particular product was used."* (Arnold Vulto)

## TRANSITIONING BETWEEN BIOLOGICALS

Transitioning from a reference biological to a biosimilar is becoming an important consideration in rheumatology practice in the EU, particularly in terms of cost savings. Analysis of data from Week 52 to Week 100 of the SB4 Phase III clinical trial demonstrated that transitioning from reference etanercept to SB4 did not result in any loss of efficacy, increase in adverse events, or increase in immunogenicity.[19] At present, there is little evidence to guide transitioning to a biosimilar in clinical practice, although real-world data are being collected. For example, the NOR-SWITCH study[20] is a non-inferiority, randomised, controlled study being conducted in Norway that is evaluating the maintenance of efficacy following transition from reference infliximab to a biosimilar infliximab (CT-P13) compared with continued treatment with reference infliximab. It is imperative that high-quality pharmacovigilance and registry data are collected when transitioning to a biosimilar.

*"We should be collecting more data directly from the patients, who are the real professionals here. They know their disease and their symptoms, and they will be the first to notice if there is a difference between what they have been receiving and what they have transitioned to."* (John D. Isaacs)

As with all medicines, patients need to be able to make a fully informed decision about whether to transition from a reference biological to a biosimilar. This includes understanding what a biosimilar is, the pharmacovigilance plan for the product, and the financial implications of transitioning. Organisations such as the International Alliance of Patient Organizations (www.iapo.org.uk) provide clear and informative materials designed to educate patients on biosimilar medications and the implications for their disease management.

*"Patients need to understand that if we can reduce the costs for some drugs, then we will have more resources available for new innovative products."* (Tore K. Kvien)

## CONCLUSIONS

*"Hopefully, with the reduced costs of these drugs, accessibility will be better so that more patients can receive an effective treatment with biologic disease-modifying anti-rheumatic drugs (bDMARDs)."* (Tore K. Kvien)

In the EU, the biosimilar development process is highly rigorous and comprehensive. Physicians can be confident that the EMA provides a thorough evaluation of each biosimilar that reaches regulatory review. Indeed, over the course of this symposium, the proportion of clinicians who would consider transitioning a patient from reference etanercept to a biosimilar increased from 54 to 73% (anonymous audience poll). Biosimilars, such as SB4, are now available in rheumatology clinical practice in the EU and are likely to improve access to rheumatology medicines, reduce costs, and, ultimately, improve health outcomes.

*"We have at least the same quality of treatment, with better access for patients, at lower cost, so a win-win everywhere."* (Arnold Vulto)

### Footnotes

(*) Enbrel® is a registered trademark of Wyeth LLC

(**) Full URL for currently-licensed biosimilars in the EU: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&keyword=Enter%20keywords&searchType=name&alreadyLoaded=true&status=Authorised&jsenabled=false&searchGenericType=biosimilars&orderBy=name&pageNo=1

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# OPTIMISING PATIENT OUTCOMES THROUGHOUT THE RHEUMATOID ARTHRITIS PATIENT JOURNEY: THE EXCEPTION, THE STANDARD, AND THE RULE

## This satellite symposium took place on 10th June 2016, as a part of the European League Against Rheumatism (EULAR) 17th annual congress in London, UK


**Chairperson**

**Peter Taylor[1]**

**Speakers**

**Ronald van Vollenhoven,[2] Peter Taylor,[1] Daniel Aletaha[3]**

*1. University of Oxford, Botnar Research Centre, Oxford, UK*
*2. Amsterdam Rheumatology and Immunology Center ARC, Amsterdam, Netherlands*
*3. Medical University of Vienna, Vienna, Austria*



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## MEETING SUMMARY


Prof Peter Taylor opened the symposium focussed on optimisation of treatment for rheumatoid arthritis (RA) at each stage of the patient's journey. Prof Ronald van Vollenhoven reviewed the evidence for first-line biologics in the 'exceptional patient' and explored which patients may be suitable for such treatments. Prof Taylor then expanded on how use of such treatments could be optimised and when to introduce biologic therapy for the so-called 'standard' patient. Finally, Prof Daniel Aletaha discussed treatment options and targets for patients who have failed on a biologic as 'the rule' in the treatment of RA.


## The Role of Biologics for Disease-Modifying Anti-Rheumatic Drugs in Naïve Patients: The Exception

### Professor Ronald van Vollenhoven

Recommendations to encourage standardisation of RA treatment were issued by the European League Against Rheumatism (EULAR) in 2010 and revised in 2013. The 2013 EULAR recommendations discourage the immediate initiation of biological therapy in combination with methotrexate but do indicate that in an 'exceptional patient' this might nonetheless be justified.[1]

Initial treatment of RA after diagnosis is recommended to be with a disease-modifying anti-rheumatic drug (DMARD); specifically, a conventional DMARD, not a biologic (Figure 1). Challenging this approach are data from several trials which provide evidence that the combination of a biologic with methotrexate is superior to first-line treatment with methotrexate alone for early RA.

The ASPIRE study was one of the first to investigate first-line anti-tumour necrosis factor (TNF) therapy in early disease.[2] Addition of infliximab (at 3 or 6 mg/kg) to methotrexate resulted in robust improvements in American

College of Rheumatology (ACR) 70% response (ACR70) at 54 weeks (33% and 37% for infliximab 3 and 6 mg/kg, respectively, in combination with methotrexate, versus 21% for methotrexate alone; both p<0.001). This was also one of the first trials to show that anti-TNF therapy combined with methotrexate is one of the most effective ways to prevent radiological damage, with mean change from baseline in Sharp/van der Heijde score of 0.4 and 0.5 for infliximab 3 and 6 mg/kg, respectively, in combination with methotrexate, compared with 3.7 for methotrexate alone (both p<0.001).[2]

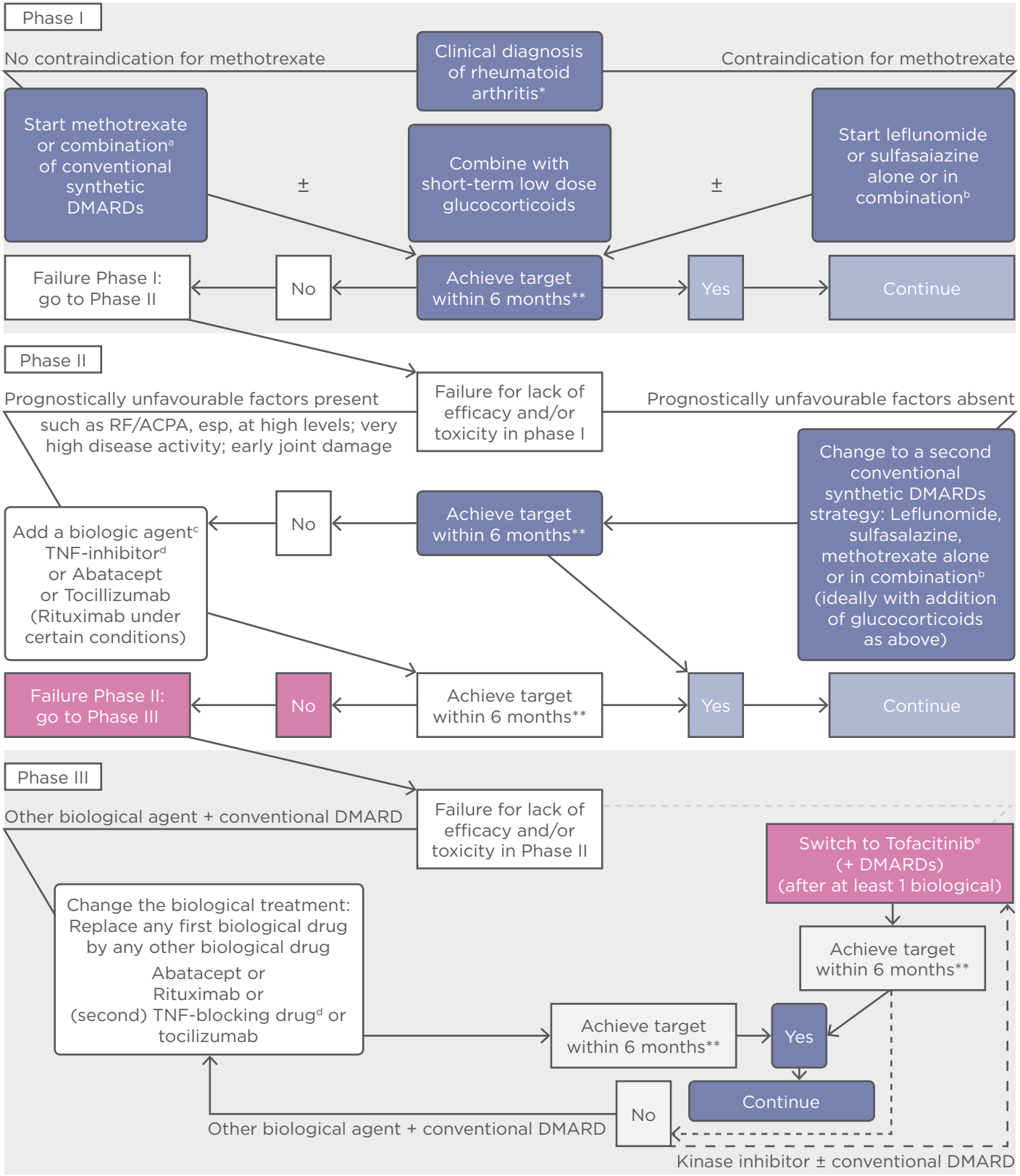


**Figure 1: Treatment algorithm based on 2013 EULAR recommendations for rheumatoid arthritis management.**

**Figure 1 continued.**

*2010 ACR-EULAR classification criteria can support early diagnosis.
**The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable at least low disease activity; the target should be reached within 6 months, but therapy should be adapted or changed if no improvement is seen after 3 months.
a) The most frequently used combination comprises methotrexate, sulfasalazine, and hydroxychloroquine;
b) Combinations of sulfasalazine or leflunomide except with methotrexate have not been well-studied, but may include combining these two and also with anti-malarials;
c) these circumstances are detailed in the text;
d) Adalimumab, certolizumab, etanercept, golimumab, infliximab, or respective well-studied and FDA/EMA-approved biosimilars;
e) where licensed.
Full black line: recommended, as shown; grey interrupted line: recommended for use after biologics failure (ideally two biologics failure); interrupted black line: recommended after two biologics failed but efficacy and safety after failure of abatacept, rituximab, and tocilizumab not sufficiently studied; black dotted line: possibly recommended but efficacy and safety of biological use after tofacitinib failure unknown at time of developing the 2013 update of the recommendations.
DMARDs: disease-modifying anti-rheumatic drugs; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; TNF: tumour necrosis factor; ACR-EULAR: American College of Rheumatology-European League Against Rheumatism; FDA: US Food and Drug Administration; EMA: European Medicines Agency.
*Adapted from Smolen JS et al.*[1]

The PREMIER study evaluated adalimumab with methotrexate compared with each treatment alone.[3] ACR70 was higher at 1 and 2 years for the combination (46% and 47%, respectively) than for methotrexate alone (28% at both time points). Again, the combination was more effective than monotherapy for preventing radiological damage.

In a further trial, comparing etanercept with methotrexate monotherapy, ACR70 was 19% and 29% for etanercept 10 and 25 mg, respectively, versus 24% for methotrexate alone at 2 years.[4] At this time point, 53% and 63% of patients treated with etanercept 10 mg and 25 mg, respectively, also had radiological non-progression (change in total sharp score [TSS] of <0.5 from baseline), versus 51% of patients treated with methotrexate monotherapy.

More recently, the C-EARLY trial evaluated certolizumab pegol + methotrexate compared with methotrexate alone.[5] The primary endpoint of sustained remission (defined as disease activity score [DAS]28-erythrocyte sedimentation rate [ESR] score <2.6 at both Week 40 and Week 52) showed statistically significant improvements with certolizumab + methotrexate versus methotrexate alone (28.9% versus 15%; odds ratio [OR]: 2.3; p<0.001). Furthermore, sustained low disease activity (LDA) (DAS28-ESR ≤3.2 at both Week 40 and Week 52) was significantly higher for certolizumab + methotrexate than for methotrexate alone (43.8% versus 28.6%; OR: 2.0; p<0.001), as was remission (DAS28-ESR <2.6) at Week 52 (42.6% versus 26.8%; OR: 2.0; p<0.001). The mean change from baseline in TSS was 0.2 for certolizumab + methotrexate versus 1.8 for methotrexate alone (p<0.001); the proportion of patients with radiological non-progression was markedly higher with the combination: 70.3% versus 49.7% for methotrexate alone (OR: 2.4; p<0.001).

A similar trial (C-OPERA) conducted in Japan showed consistent results at 1 year.[6] DAS28-ESR remission (score <2.6) rates were 57.2% for the combination certolizumab pegol + methotrexate versus 36.9% for methotrexate alone (p<0.001). Simple Disease Activity Index (SDAI)-based remission (score <3.3) rates were higher for the combination (57.9% versus 33.8%; p<0.001), as were Boolean-based remission (tender joint count ≤1 in 28 joints, swollen joint count ≤1 in 28 joints, C-reactive protein ≤1 mg/dL, and Patient's Global Assessment of Disease Activity ≤1) rates (45.3% versus 28.0%; p<0.01). The U-ACT-EARLY trial also showed comparable results combining tocilizumab with methotrexate.[7] The combination was superior in terms of sustained remission rates (DAS28 <2.6 and swollen joint count ≤4, sustained for ≥23 weeks with the exception of ≤2 visits at which DAS28 could be ≥2.6 but <3.2) which were 86% for the combination versus 44% for methotrexate alone.

Given the available evidence, it could be questioned why the combination of MTX and biologics is not routinely recommended in first-line therapy. Firstly, a combination strategy would clearly over-treat some patients (an estimated 30% of RA patients), since some would do well with monotherapy. Secondly, medical risks are greater for combined treatment, since each drug has its own potential side effects. Thirdly, and probably most importantly, there is a large cost difference between combination therapy and methotrexate monotherapy. Lastly, some studies have suggested that longer-term results may be equal if conventional DMARDs are started first and biologics added later. In the BeST trial, immediate treatment with infliximab + methotrexate showed better remission rates in the first year compared with immediate treatment with methotrexate + prednisone, sequential monotherapy, or step-up therapy.[8] But long-term outcomes over 7 years were similar, as patients in the other three groups could also receive methotrexate + anti-TNF therapy.

For these reasons, first-line biological therapy should not routinely be considered. Nonetheless, first-line biological might be considered for patients with high inflammatory burden, allowing rapid relief of symptoms, and for those at highest risk of irreversible radiological damage. It may also be considered for patients for whom the only other rapidly-acting alternatives, glucocorticoids, are contraindicated.

A potential future strategy is induction-maintenance therapy. The OPTIMA trial evaluated induction therapy with adalimumab + methotrexate or placebo + methotrexate followed by a continuation/withdrawal phase for patients achieving stable LDA after 26 weeks.[9] For patients who stopped adalimumab, remission rates (DAS28 <3.2) decreased only slightly. In Phase II of the C-OPERA study, patients initially treated with certolizumab + methotrexate received maintenance with methotrexate alone after 1 year.[10] At 2 years, SDAI-based remission rates remained higher in patients initially treated with the combination than in those initially treated with methotrexate alone (41.5% versus 29.3%; $p<0.05$), as did rates of radiological non-progression (84.2% versus 67.5%; $p<0.001$). In the PRIZE study, all patients received open-label etanercept + methotrexate for 52 weeks and were then randomised to etanercept + methotrexate, methotrexate alone, or placebo.[11] A lasting benefit in DAS28 remission was observed after biologic was stopped. The induction-maintenance strategy is also currently under investigation in the C-EARLY trial.

In conclusion, first-line use of biologics is not recommended for routine use, but may be an appropriate medical choice in exceptional cases. In the future, induction-maintenance using biologics as first-line therapy may prove to be a highly effective and cost-effective alternative to the current treatment paradigm, but further studies are needed.

## When to Start Biologics: The 'Standard Patient'

**Professor Peter Taylor**

Both ACR and EULAR recognise the importance of regular assessment of patients, evaluating disease activity, treating appropriately, and escalating therapy when required, with a view to attaining the aspirational targets (remission or LDA).[1,12] Treating patients early with effective therapies achieves remarkably high and sustained remission rates. However, in the clinic, some patients will never achieve aspirational targets.

Detailed recommendations are available for optimising pharmacological therapy, but optimising the patient through lifestyle interventions or adaptation should also be considered. Phenotypic expression of RA has become less severe in recent decades, possibly because of reductions in smoking at the population level. An epidemiological study in an early RA cohort from Sweden showed that both current and past smokers are less likely to have good response either to methotrexate or TNF inhibition.[13] In the SWEFOT trial, smoking was a predictor of rapid radiographic progression at 1 year (Sharp/van der Heijde score increase ≥5) in DMARD-naïve RA patients treated with methotrexate, with an OR of 2.25 for current versus never smokers, and 2.67 for current versus non-smokers.[14] Smokers also have a greater likelihood for poor functional progression.[15] Therefore, patients should be advised not to smoke; given that RA has heritable components, this advice should also be extended to patients' children.

Obesity also has an effect on RA pathobiology and response to therapy. In a prospective study, overall quality of life measured by total Medical Outcomes Study short form 36 score was lower among obese

RA patients than in normal or overweight patients, as were physical and mental components.[16] Data from the Swedish cohort also showed that the likelihood of achieving LDA or EULAR good response at 6 months is lower for overweight or obese patients than patients of normal weight, with OR for LDA, EULAR good response and remission of 0.49, 0.50, and 0.58, respectively.[17] Therefore, advice about lifestyle issues (smoking and weight loss) is important, emphasising the role of the multidisciplinary team beyond pharmacological intervention.

EULAR recommends that methotrexate should be part of the first treatment strategy for patients with active RA.[1] Methotrexate is a highly effective agent, both as monotherapy and in combination with glucocorticoids, other conventional synthetic DMARDs (csDMARDs) and biological DMARDs (bDMARDs), and serves as an anchor drug in RA. As monotherapy with or without glucocorticoids, it is effective in DMARD-naïve patients and leads to LDA or ACR70 response in 25–50% of patients within 6–12 months. Early response is a strong indicator of sustained response. Emerging data from the C-EARLY study with optimised methotrexate (initiated at 10 mg/week and rapidly escalated to maximally tolerated dose) suggested that patients who fail to achieve a response (as little as DAS28 improvement of 0.6) by 12 weeks are unlikely to do well at 1 year.[18] Therefore, one might consider step-up treatment at an early time point of 3 months.

The CONCERTO study was a randomised, double-blind, parallel-armed study of methotrexate in combination with adalimumab to assess whether an increasing trend of efficacy and decreased safety exists when increasing methotrexate dose.[19] This study showed that doses of 10 or 20 mg/week in combination with the biologic confer equivalent benefit in terms of radiographic non-progression (change in modified TSS ≤0.5; 76.8% versus 77.6% of patients) and comprehensive disease control (defined as DAS28-C-reactive protein <2.6, Health Assessment Questionnaire-Disability Index <0.5, and change in modified TSS ≤0.5; 21.2% versus 26.5% of patients). Therefore, if a patient cannot tolerate escalation of methotrexate dose, it may be possible to continue methotrexate at a lower dose with nearly all the benefit.

Another issue with methotrexate is that bioavailability of oral treatment is not linear across the 10–25 mg dose range.[20] Subcutaneous methotrexate shows linear exposure, and has been associated with better treatment survival than with oral therapy, with treatment failure rates at 1 year of 49% and 77%, respectively (p<0.0001).[21]

Since methotrexate is a folic acid mimetic, concomitant folic acid should be given. Patient education is important, as folic acid supplementation is associated with better survival on methotrexate, adherence, and outcomes.[22] Benefits of folic acid supplementation also include a 26% relative risk reduction for gastrointestinal side effects (p=0.008), 76.9% relative risk reduction for serum transaminase elevation (p<0.00001), 60.8% relative risk reduction for withdrawal from methotrexate for any reason (p<0.00001), and 28% relative risk reduction for stomatitis (not significant).[23]

EULAR recommendations state that, in DMARD-naïve patients, csDMARD monotherapy or combination therapy of csDMARDs should be used, irrespective of the addition of glucocorticoids.[1] Several additional studies suggest that csDMARD combinations are superior to methotrexate monotherapy, with some showing efficacy to be similar to that of bDMARDs, suggesting that this could be a more cost-effective option. Although these trials yielded similar results, controversy persists because of the methodological limitations of these studies. Moreover, recent data suggest that sequential monotherapy is as effective as combination therapy in clinical, functional, and structural outcomes, and that stepping up from methotrexate monotherapy to a biological agent has significant superiority over a combination of csDMARDs.

The SWEFOT study showed a numerical, but not statistically significant, trend for higher EULAR good response with bDMARD (infliximab) + methotrexate than with csDMARD (sulfasalazine + hydroxychloroquine) + methotrexate among RA patients who failed methotrexate treatment (39% versus 25% at 12 months, 38% versus 29% at 18 months, 38% versus 31% at 24 months).[24] The RACAT study was a non-inferiority trial in which patients with active RA were randomised to triple therapy (sulfasalazine + hydroxychloroquine + methotrexate) or etanercept + methotrexate.[25] Patients who did not respond switched to the other therapy at 24 weeks. DAS28 remission (score ≤2.6) was 12.7% for triple therapy versus 21.7% for etanercept + methotrexate at 24 weeks (p=0.03), and 20.8% versus 25.2% at 48 weeks (not significant); ACR70 response was 5.0% versus

16.0% at 24 weeks (p=0.001) and 18.1% versus 26.5% at 48 weeks (p=0.08).

csDMARD combinations may be more efficacious than csDMARD monotherapy in early RA.[26] Escalating treatment from csDMARD monotherapy to combination therapy is effective in a high proportion of early RA patients.[24] This may be cheaper than escalation to bDMARD therapy and csDMARD combination therapy may be associated with a better tolerability profile than bDMARD therapy.

Current EULAR recommendations state that bDMARDs should be started when patients have not achieved the therapeutic target after treatment with csDMARDs for 6 months (or had no improvement at 3 months).[1] Although the armoury of effective drugs for RA has expanded significantly, particularly for biologics, the lack of head-to-head studies makes it difficult to choose between them.

In conclusion, with respect to the 'standard' patient, it is important to optimise the methotrexate dose and mode of delivery with a view to the ratios of benefit-to-risk to tolerability and persistence on the drug. Emerging data suggest that failure of clinical response to methotrexate by 3 months strongly predicts failure to achieve remission or LDA target with methotrexate at 1 year. Patients can be assisted to feel empowered to help themselves achieve the best response to therapy by optimising their weight and by smoking cessation. Simple education and reminders to take folic acid supplementation can help persistence on methotrexate and significantly reduce gastrointestinal toxicity and hepatotoxicity.

## How to Optimise Biologics: The Rule

### Professor Daniel Aletaha

Optimisation of treatment involves setting a clear target for response, creating a plan to assess progress and adjusting the approach when required.[1] When setting the target, we must first ask what the target should be. Remission criteria endorsed by ACR and EULAR (Table 1) involve two categories: full criteria for clinical trials, and adapted criteria for clinical practice (without acute phase reactants).[27,28] Within these, there are also two methods of determining remission: Boolean (which involves intersection of clinical criteria, all of which must be fulfilled) and index-based (which involves the sum of criteria, allowing compensation for one variable not being in remission if all other variables are).[29]

The critical target is the one that predicts for prevention of disease progression. The Boolean set of criteria was shown to have a positive likelihood ratio of good outcome of 2.9 if remission criteria are fulfilled, whereas the DAS28 <2.6 has a lower positive likelihood ratio of 1.0 for a good outcome, because patients with DAS28 response may still have swollen joints.[27] Decreasing the cut-off point for DAS28 to <2.0 slightly increases the positive likelihood ratio to 1.6. The highest positive likelihood ratio for a good outcome is given by the SDAI ≤3.3, at 3.0.

Recommendations dictate assessment at 3 and 6 months,[1,12] but the right time point for considering changes to therapy is less clear. At 3 months, if the patient is in remission, therapy is working and should be continued. If the patient's disease activity is unchanged, treatment must clearly be adapted. Patients not reaching the target but showing improvement at 3 months pose a greater challenge. If the patient has achieved major response criteria (SDAI 85%, EULAR good response, or ACR70), they are likely on track to achieve the selected target.[30] However, if they fail to meet minor response criteria (SDAI 50%, EULAR moderate response, ACR20), they will likely never reach the remission target at 6 months.

Once the decision has been made to adjust treatment, the question becomes which drug shall we use? Response rates to different drugs with different modes of action are remarkably similar across phases of treatment, and the decision is made more difficult by a lack of head-to-head studies.

The EXXELERATE study[31] is the first head-to-head study comparing the efficacy and safety of two TNF inhibitors in patients who are primary non-responders to the alternate therapy (Figure 2). Preliminary data (not yet published) indicate that there is no difference.

Why do compounds with different modes of action appear to produce similar response rates in patients with methotrexate failure?[32] The first explanation is the bottleneck hypothesis: that all current 'targeted therapies' interfere with a common final pathway ('bottleneck of inflammation') and therefore we deal mostly with one major responder pool.[33] The second explanation posits that responders to each of the different modes of

action do not overlap completely; some patients may respond preferentially to one treatment over another. This explanation forms the basis of precision medicine, i.e. 'delivering the right treatment at the right time, every time, to the right person'.

More patients are achieving remission and the question is then what to do if the target is reached, as stopping treatment may lead to secondary treatment failure. Approximately 34–43% of patients will be in remission at one visit, but the rate of sustained remission reduces to approximately 17–20% after a second visit.[34] Sustained remission is important, since function continues to improve over time in patients who maintain remission.[35]

The importance of detection of subclinical synovitis in evaluating initial and sustained remission is unclear. Presence of subclinical synovitis (power Doppler signal positive) is associated with an OR for radiographic progression of 12.21 ($p<0.001$).[36] Ultrasound signals are highly sensitive and sonographic findings can take years to normalise.[37]

**Table 1: Remission criteria for clinical trials and clinical practice.**

| | For clinical practice[27] | For clinical trials[28] |
|---|---|---|
| **Boolean criteria** | SJC ≤1<br>TJC ≤1<br>PtGA (0–10 scale) ≤1 | SJC ≤1<br>TJC ≤1<br>PtGA ≤1 (0–10 scale)<br>CRP ≤1 mg/dL |
| **Index-based criteria** | CDAI ≤2.8<br>Where CDAI=SJC in 28 joints + TJC in 28 joints + EGA + PtGA[29] | SDAI ≤3.3<br>Where SDAI=SJC in 28 joints + TJC in 28 joints + EGA + PtGA + CRP (in mg/dL)[29] |

CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; EGA: evaluator global assessment; PtGA: patient global assessment; SDAI: Simple Disease Activity Index; SJC: swollen joint count; TJC: tender joint count.

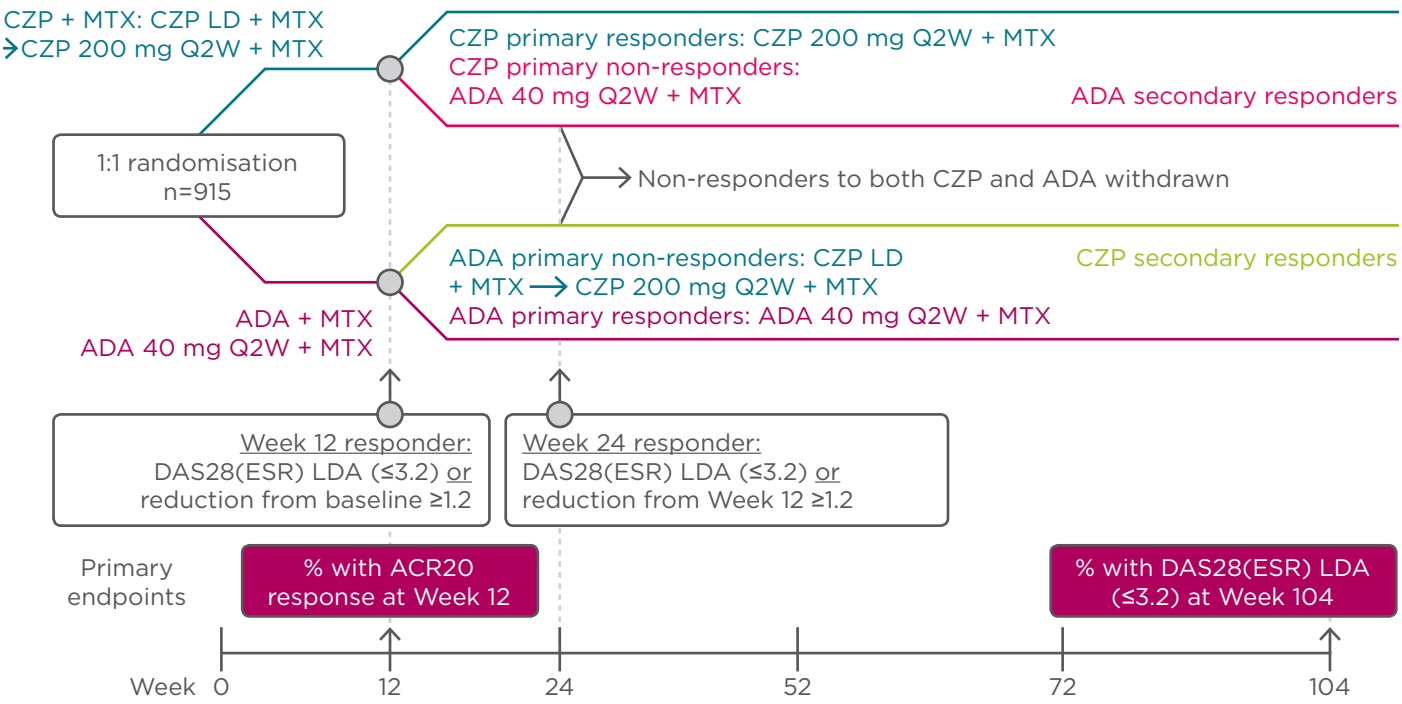


**Figure 2: EXXELERATE study design.**
ACR20: American College of Rheumatology 20% improvement; ADA: adalimumab; CZP: certolizumab pegol; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; LD: loading dose; LDA: low disease activity; MTX: methotrexate; Q2W: every 2 weeks.

There is currently no clinical evidence to support a change in treatment based on subclinical signs.

EULAR recommendations for tapering biologic treatment state that, if a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs, especially if treatment is combined with a csDMARD.[1] Tapering biologics (decreasing dose, or increasing intervals between doses) is better than stopping the drug. In the PRESERVE study, patients with sustained LDA on etanercept 50 mg weekly + methotrexate weekly from Weeks 12–36 were randomised to continue full dose etanercept, half dose etanercept, or placebo.[38] There was no difference between the full and half dose, but remission was much lower in the group that completely stopped etanercept. Tapering was also investigated in the C-EARLY study, where patients with sustained remission at Week 40 and 52 on certolizumab pegol 200 mg every 2 weeks + methotrexate were randomised to continue certolizumab pegol every 2 weeks, reduce dosing to every 4 weeks, or to stop certolizumab pegol.[5]

In conclusion, treat-to-target is the key concept for management of RA. In addition, a management strategy for RA needs to include guidance regarding which compound to select over another: sufficient data to support definitive recommendations are still awaited. Reaching the target of remission is only the first step, sustaining remission is the goal. In sustained remission, any drug tapering needs to be undertaken with caution, with appropriate opportunities to evaluate response built into the management plan.

## Panel Discussion

### Chaired by Professor Peter Taylor

***Q:*** Is the added benefit of targeted therapies lower in DMARD-naïve (very early RA) patients?

**A:** There is no question that methotrexate + a biologic is superior to methotrexate alone in early RA, but methotrexate alone is also very effective. Trials describe outcomes at the group level. For an individual patient, a dramatic improvement may be seen with the switch from DMARDs to DMARDs + biologic; it is uncertain if the reverse is also true, but it could be possible for an individual patient. In the future, the hope is that we can individualise treatment better.

**Q:** Why escalate the dose of methotrexate instead of starting at a higher dose? Can we obviate the need for biologics by starting corticosteroids early?

**A:** It takes time for methotrexate to work and most guidelines recommend use of low-dose corticosteroids. The key issue for the risk-benefit profile is how much do you give at the beginning?

Patients who have control on methotrexate do not need biologics, whereas those who do not are perceived to have 'lost' 3–4 months. There is also the potential for radiologic damage, although this is likely to be minimal. While we know that combination is better than monotherapy, starting with monotherapy then stepping up to combination therapy can achieve the same clinical outcomes whilst avoiding overtreatment of patients who benefit from methotrexate alone.

Early induction with corticosteroids can provide rapid symptomatic benefit, but it is important to consider that corticosteroids have serious tolerability issues, particularly the risk of infections and serious infections. Trials are currently ongoing to assess the risks and benefits of combining methotrexate with a corticosteroid or a biologic, compared with methotrexate alone.

**Q:** After therapy with the first anti-TNF agent, which mechanism of action is recommended? Is it worth trying another anti-TNF agent?

**A:** Data from registries and observational studies suggest that a second anti-TNF agent may be as effective as any other mechanism of action.

**Q:** Bearing in mind differences across health economies in the threshold for access to a biologic, what are some pointers to the 'exceptional patient' who would merit early introduction of a biologic?

**A:** Patients with high disease activity and risk factors for rapid progression may warrant immediate treatment with a biologic. It is also important to consider the patient preference: whether they are prepared to wait for response or require rapid symptom relief. Models to evaluate the number needed to treat may also be beneficial.

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# HOW PATIENT VALUE CAN INFORM CLINICAL AND RESEARCH STRATEGY

In a fast-evolving healthcare environment, with many new innovator drugs and mechanisms of action, entry of biosimilars, and increasing constraints on healthcare budgets, the patient remains the constant factor.

Current EULAR treatment guidelines highlight the need for shared treatment decisions between patient and rheumatologist.[1] With such patient empowerment comes the need for individuals to be able to fully understand the implications of their condition, as well as the rationale for, and consequences of, different management strategies. Central to the interaction between rheumatologist and his/her patient is the need to understand which element of disease and/or other factor(s) need to be 'restored' to enable a patient to reach a near normal state, which could be termed as delivering 'patient value'. Delivering patient value is critical in both drug development and patient management, and requires an appreciation of a multitude of factors, including particular patient beliefs/preferences, patient history and knowledge of the individual, the disease type/sub-type, and finally the stage and severity of symptoms.


**Figure 1: Theoretical framework to help define patient value. Abstraction of obtained results, UCB Patient Value Survey, May 2015.**

In an effort to advance the understanding of the relative importance of these multiple factors, a survey was conducted by UCB in 450 European Union patients with RA, axial spondyloarthritis, and psoriatic arthritis, with the majority having been treated for up to 10 years. The survey was based on a theoretical framework to evaluate patient value, exploring different dimensions of the patient experience that may be impacted by disease (Figure 1):

1. Physical symptomatic
2. Mental and emotional
3. Social
4. Economic impact (i.e. work productivity and cost of care)
5. Disease impact on family/spouse (e.g. burden on family, dependency for help, etc.)

In the section focussing on 'Understanding the Patient', the survey found that patients still suffer from active inflammatory symptoms on a daily basis, despite being treated with biologics (31%), disease-modifying anti-rheumatic drugs (41%), non-steroidal anti-inflammatory drugs (54%), or corticosteroids (24% [UCB data on file]). The impact of disease varied by region, as well as across diseases, with axial spondyloarthritis patients experiencing a higher degree of impact of their symptoms. Not surprisingly, pain featured prominently on the reported symptoms, despite all patients being treated in line with standard recommendations. Inability to perform daily tasks, joint tenderness, stiffness, and fatigue were the next most highly rated aspects. Also prominent were anxiety and depression, which were each mentioned by over a third of all patients. In terms of importance and impact on patient life, physical symptoms were followed by mental and social aspects, with mental health issues (depression and anxiety) being experienced by over a third of patients (Figure 2). Patients expressed feeling frustrated and powerless due to their condition, which could both be major factors influencing impairment of quality of life and a suboptimal patient experience. It appears that although clinicians have powerful tools in the medical armamentarium to tackle the inflammatory

burden of rheumatic disease, symptoms of pain, anxiety, and depression may often not be adequately addressed.

The question was asked: "Please indicate which 'impact on life' you consider to be 'most concerning' and which one is the 'least concerning'." Scores were indexed against the attribute receiving the highest score (pain) which was given a score of 100, e.g. less energy causes have as much concern as pain. Data shown demonstrates the percentage of the attributes chosen as most important across the survey. There was a total of 451 respondents (country bases: UK n=91, France n=90, Germany n=90, Italy n=90, and Spain n=90).

Rheumatologists (N=141) attending EULAR in Rome 2015 were asked many of the same survey questions asked to patients. While not a matched-control to the patient survey, a marked disconnect was apparent in patient-doctor perceptions of 'patient value'. There was good patient-physician consensus on the need to address and contain the physical impact of the disease; however, rheumatologists saw the emotional burden of the disease, clearly identified by patients as being in need of attention, as very low on their care priority list.

The key insight here is that patients, whilst being adequately medically treated according to today's standards, still suffer 'collateral symptoms', which could be addressed by marginally broadening the therapeutic focus. These initial findings may fuel further research into specific disease areas, as well as exploration of tailored solutions that may make a difference to patients in their quest to restore near-normality to their lives. The end goal of shared decision-making may be that, by considering these 'collateral symptoms' when treating rheumatic diseases, clinicians may impact a patients journey more via pharmacological and non-pharmacological solutions and address needs in a manner that truly, and more holistically, delivers patient value.

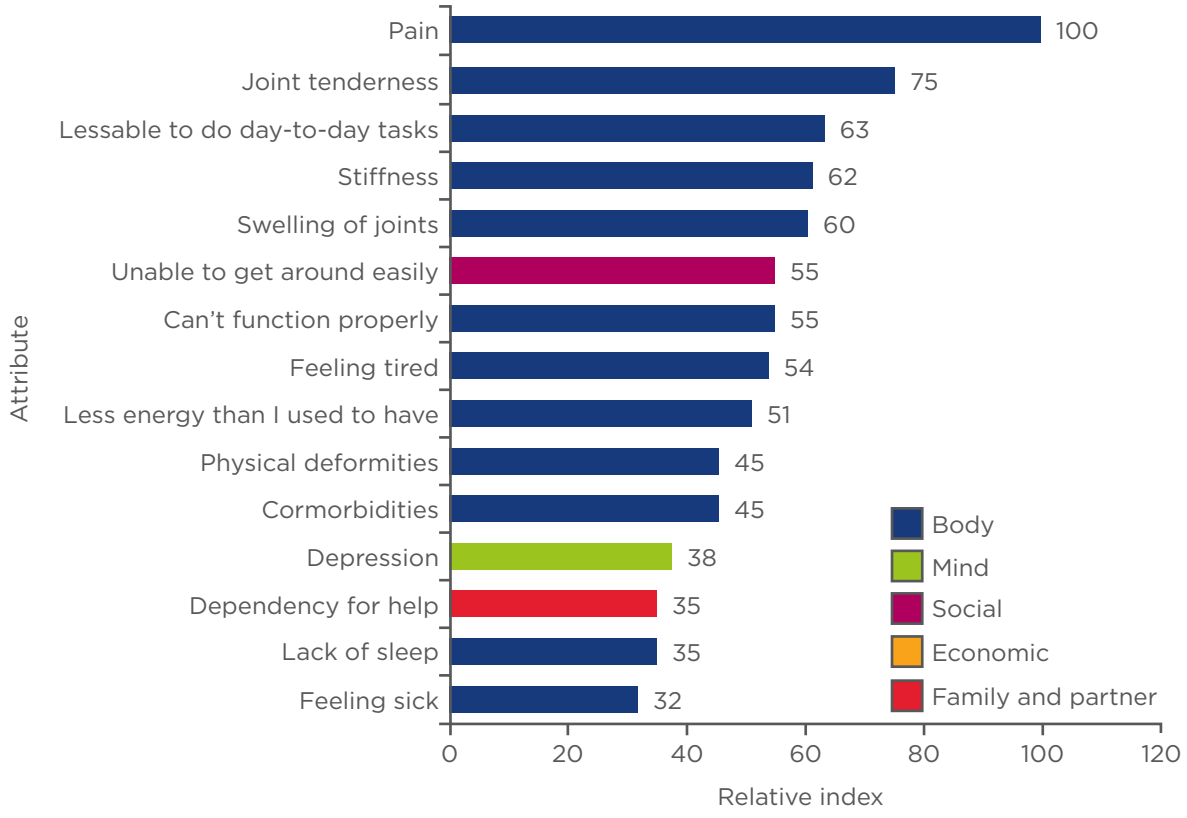


**Figure 2: Top 15 relative attributes of importance to rheumatology patients. Abstraction of obtained results, UCB Patient Value Survey, May 2015.**

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# UNRAVELLING THE MYSTERY BETWEEN STRUCTURE AND SUSTAINED CLINICAL OUTCOMES

## This symposium took place on 9th June 2016 as a part of the European League Against Rheumatism (EULAR) Congress 2016 in London, UK


**Chairperson**

**Edward Keystone[1]**

**Speakers**

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## MEETING SUMMARY


Targeted biologics have revolutionised the treatment and outlook of patients with inflammatory joint diseases. The combination of high-cost long-term therapy straining healthcare systems with impending expiry of key biologics patents has led to heightened interest in the development of biosimilars. The expanding landscape of biosimilars has triggered, in healthcare providers, the need to explore the option to non-medically switch stable patients from costly reference products to less expensive alternatives. Currently, there are many unknowns surrounding the effects of non-medical switching on patient outcomes and cost-effectiveness. Prof Edward Keystone opened the symposium by discussing the constantly evolving landscape of biologics, highlighting that their high cost is becoming an increasing challenge and has created the issue of non-medical switching. Dr Leigh Revers provided a background to the structural and functional relationships of biologic therapies, stressing the need for careful control of the manufacturing processes of these large and complex molecules. Prof Keystone presented the long-term data currently available for anti-tumour necrosis factor (anti-TNF) agents and examined how sustainability of response can be influenced by multiple factors. Prof Thomas Dörner concluded the symposium by stressing the importance of the prescribing doctor being in control of which biologics their patients receive to ensure effective pharmacovigilance. The challenge of non-medical switching was discussed along with the potential trial designs that could help to determine if biologics and biosimilars could be interchangeable.

## How Biologics Work: What We Know and What We Do Not Know

### Professor Edward Keystone

Biologics have changed the landscape of modern therapy for inflammatory diseases. For patients that fail conventional disease-modifying anti-rheumatic drugs, biologics can provide a substantial reduction of disease signs and symptoms, a significant inhibition of radiographic progression and joint damage, and improvements in quality of life.

There are currently three classes of TNF inhibitors: recombinant receptor/Fc fusion proteins (etanercept), monoclonal antibodies (infliximab, adalimumab, golimumab), and PEGylated Fab' fragment (certolizumab pegol).[1] Some of the newer biologics include: rituximab, an anti-B cell chimeric monoclonal antibody; abatacept, a co-stimulation blocker recombinant fusion protein; and tocilizumab, an anti-interleukin-6 recombinant humanised monoclonal antibody.[2]

Despite biologics being available to treat rheumatic diseases for some time, there are still many unknowns. Biomarkers or reliable predictors of response are needed, as well as a sustained response leading to cure and reversal of pre-existing joint damage. A key challenge surrounding the use of biologics is payer restriction. The issue of increasing healthcare costs in the UK highlights the need for more affordable therapies. In 1997, the total healthcare expenditure was £54.9 billion, a value that has risen every year until 2013.[3]

The introduction of lower cost biologics has raised the issue of non-medical switching between therapies. Medically-driven switching occurs when patients have had an inadequate response or experienced an intolerable adverse event to a biologic.[4,5] Non-medical switching occurs when a patient has an adequate response and has tolerated treatment well, but a desire for cost saving or patient preference drives the decision.[6-8]

The potential cost-saving benefits of non-medical switching have not been established. A study by Liu et al.[6] comparing total medical costs for patients that were maintained on treatment and those that switched from adalimumab to another injectable biologic, reported that non-medical switching increased healthcare costs.[6] These initial data suggest that the issues of costly biologics are not necessarily addressed with a switch to cheaper treatments. Currently there is insufficient robust evidence to provide a definitive answer regarding the effects of non-medical switching.

## Structural to Function Relationship of Monoclonal Antibody Therapies

### Doctor Leigh Revers

A wealth of experience of using biologics to effectively treat rheumatoid arthritis (RA) patients is available;[9] however, with the changing treatment landscape there is a need for physicians to be better informed about the development of biologics and how they differ from the more conventional small molecule drugs that are prevalent in pharmacopoeias.

Biologics are best described as pharmaceutical ingredients derived from living organisms that cannot reasonably be synthesised by chemical means. However, the synthesis of such complex biologic molecules could one day be a reality: a study published by Wang et al.[10] in 2013 reported the first total chemical synthesis of erythropoietin, a less complex biologic than a monoclonal antibody.

The history of biologics began in 1921 with the discovery of insulin by Banting and Best in Toronto, Canada, which led to approval of the first biotech drug, insulin isophane, by the US Food and Drug Administration (FDA) in 1982. The first glycoprotein biologic, epoetin alfa was developed in 1989, followed by the humanised monoclonal antibody, daclizumab, from Roche in 1996, and the human monoclonal antibody, adalimumab, from AbbVie in 2002. Over the past decade, numerous more biologics have become available, creating a complex market.[11]

Small molecule drugs are synthetic and uniform, making them predictable and easy to characterise. Biologics however, are biosynthetic molecules that are large and heterogeneous, with a 3-dimensional structure, making them more complex, sensitive, and difficult to fully characterise. The high cost of biologics has led to the development of biosimilar molecules. A biosimilar is an approved, new version of an innovator biologic, following patent expiry that has undergone rigorous comparability tests and shows no clinical differences. The term

'biosimilar' used by the European Medicines Agency (EMA) reflects that they recognise possible non-equivalence and structural differences between reference products and biosimilar agents.

The manufacture of biologics and biosimilars follows the same broad steps: development of a host cell, establishment of a master cell bank, production of protein, purification, analysis, and formulation prior to storage and handling.[12] Manufacturing of both biologics and biosimilars requires high levels of control over the organism used to prepare the molecules. The process of transcription and translation from DNA is a reliable process to create the proteins needed.

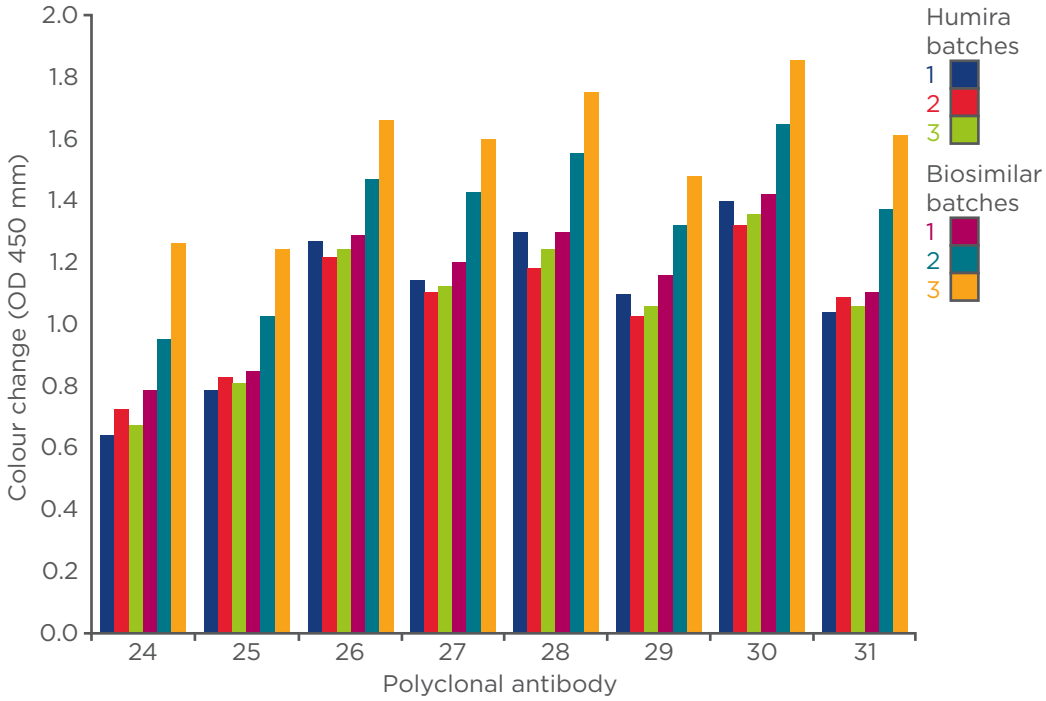


**Figure 1: Inconsistencies between adalimumab and non-approved biosimilar monoclonal antibodies in the constant region-2.[16]**
OD: optical density.

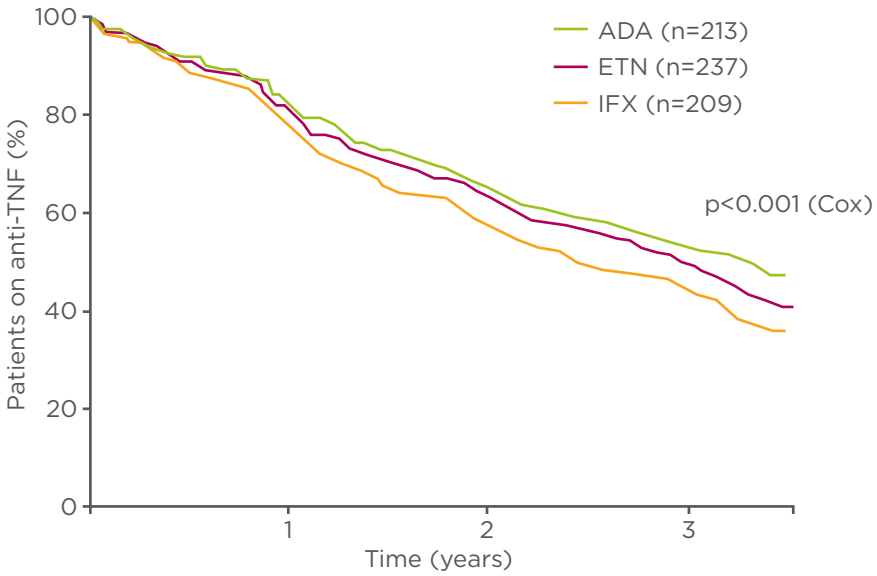


**Figure 2: Comparison of drug retention rates between anti-tumour necrosis factor therapies in rheumatoid arthritis patients from the Swedish Clinical Quality Management – Rheumatoid Arthritis registry.[29]**
ADA: adalimumab; ETN: etanercept; IFX: infliximab; anti-TNF: anti-tumour necrosis factor.

Post-translational modification of proteins, however, is difficult to replicate and the sponsor of a biosimilar will never have access to the innovator's host cell. The addition of branched sugar molecules to proteins involves many different enzymes and follows no template.[13] Glycoforms are glycoprotein molecules with the same protein component but different assemblies of sugar chains, hence why all antibodies produced are a complex mixture of products.[14]

The challenge for the manufacture of biosimilars is the lack of detailed, publicly available information regarding the manufacturing process of biologics. The synthesis of biologics often undergoes manufacturing changes over time for a variety of reasons, e.g. to upscale production; these manufacturing changes significantly differ from the biosimilarity exercise as for such small process changes, only quality and analytical studies are required to evaluate the product. The manufacture of biosimilars will have fundamental differences to biologics, such as a different cell-line and a knowledge gap in the synthesis process of the innovator. Regulators require comparative clinical studies to ensure that differences between biosimilars and the reference biologic do not translate into differences in efficacy and safety.[15]

The rapidly increasing numbers of manufacturers of biologics could affect product consistency. Many quality attributes are measured for biologics; an inherent drift in manufacturing is expected to either cause a divergence or convergence of these attributes. There are reports of inconsistencies between originator and non-approved versions of biosimilars in the literature. Wang et al.[16] found differences in higher order structure comparability of adalimumab and biosimilar monoclonal antibodies in the constant region-2 using an antibody array enzyme-linked immunosorbent assay (ELISA) (Figure 1), with similar results on trastuzumab. These results raise concerns over variability in the antigenicity and therefore the potential immunogenicity of biosimilars.[16] Independent research in the USA examined glycoforms of infliximab and biosimilar CT-P13 and reported differences between the two molecules related to the addition of fucose.[17]

In conclusion, biologics are larger and more complex than conventional chemical drugs, and can only be synthesised organically. Biosimilars cannot be described as generics, but as substances similar in structure to originator biologics. The complex post-translational modifications of monoclonal antibody biologics create a key challenge for biosimilar manufacturers. Slight alterations in the manufacturing process can lead to clinically relevant changes, particularly related to potency. The imminent expiration of some key biologic patents is driving the increased development of less costly biosimilars. All biosimilars that come to the market, however, should be closely monitored and evaluated before and upon approval.

## What We Know: Evidence on Long-term Data and Immunogenicity

### Professor Edward Keystone

Numerous clinical trials have documented the long-term response of patients to anti-TNFs. The sustainability of biologics can be affected by a variety of factors including: the development of drug-drug antibodies, the combination of biologics with methotrexate, the number of biologics a patient has been treated with previously, baseline disease activity, and the nature of biologics in TNF inadequate responders. Early use of biologics can also have an impact on sustainability of response, with patients treated early tending to do better than those in whom treatment was delayed.[18-24]

Vincent et al.[25] performed a systematic analysis of studies measuring the development of anti-drug antibodies to a range of anti-TNF biologics. For infliximab, the 26 studies analysed covered a range of rheumatic diseases and had a large variation in duration, ranging from 2 to >360 weeks. Anti-infliximab antibodies developed in 6–61% of all patients, and in 10–50% of RA patients, specifically. These numbers reflect those seen in the clinic with infliximab monotherapy. The other biologics analysed in the study, adalimumab, etanercept, certolizumab, and golimumab, also demonstrated a wide range in the rate of anti-drug antibodies developed.[25]

Collectively, the data regarding anti-drug antibodies shows that all anti-TNF therapies may be associated with the appearance of such antibodies. However, the large variability in the number, design, and duration of studies assessing anti-drug antibodies, as well as the techniques used for detection, should be taken into account. Currently, there are a number of

methods available to detect anti-drug antibodies, ranging from standard direct/indirect enzyme-linked immunosorbent assays to homogenous mobility shift.[25-27] The development of more sensitive methodologies has translated into an increase in the number of anti-drug antibodies detected. The study by Bartelds et al.[28] in 2011 assessed the effect of anti-adalimumab antibodies on sustained disease activity and remission in 200 patients. The results showed a significant correlation between anti-drug antibodies, clinical response, and sustainability of this response.[28]

The durability of response to biologic treatment in rheumatologic diseases has been characterised; registration studies and surveillance databases provide ≥5 years of data*.[29-31] The ARTIS study reported higher discontinuation rates in infliximab-treated patients compared with adalimumab and etanercept. Etanercept showed the greatest sustainability with 55% of patients remaining on treatment at the end of 5 years.[31] The DANBIO study of biologic monotherapy-treated patients also found that etanercept had the greatest adherence rate (56%) and infliximab the least (41%), at 4 years.[30] The Swedish Clinical Quality Management (SCQM)-RA registry reported significant differences in rates of discontinuation between anti-TNF therapies. However, in this study, adalimumab-treated patients showed the greatest attrition to therapy (Figure 2).[29]

Long-term treatment with the biosimilar CT-P13 (biosimilar of the infliximab reference product) has been analysed in the PLANETRA study. The study reported clinical responses and immunogenicity in comparison with infliximab. At 54 weeks, the response was similar between both therapies, while 52.3% and 49.5% of CT-P13 and infliximab-treated patients were positive for anti-drug antibodies, respectively. Interestingly, both therapies displayed an approximate 20% decrease in American College of Rheumatology (ACR) criteria for 20% improvement (ACR20) response if either positive or negative for anti-drug antibodies.[32] In the extension phase of the PLANETRA study, infliximab-treated patients were switched to CT-P13 for a further 48 weeks. At the end of study (102 weeks), the number of patients achieving ACR20 was similar between the CT-P13 maintenance group and the infliximab to CT-P13 switch group (71.7% and 71.8%, respectively). In the maintenance group, 40.3% of patients were positive for anti-drug antibodies, compared with 44.8% in the infliximab to CT-P13 switched group.[33]

In conclusion, rheumatic patients can achieve a sustained response with biologic therapies, and long-term data for anti-TNF biologics continue to emerge. The sustainability of anti-TNF biologics can be influenced by several factors, including immunogenicity. Due to the complex and evolving biologic treatment landscape, the challenge of how to clinically inform and follow up non-medical switching between therapies needs to be addressed, and more rigorous data are needed to inform patients with sustained clinical responses about non-medical switching.

## What We Do Not Know: Data Generation Needs to Support Switching of Stable Patients

**Professor Thomas Dörner**

The definitions used to describe treatment of patients with biosimilars can vary between regulatory bodies, physicians, and pharmacists. 'Interchangeability' is a status given to a product and decided by regulatory agencies. The FDA define it as "an interchangeable biologic product, in addition to meeting the biosimilarity standard, is one that is expected to produce the same clinical result as the reference product in any given patient."[34] The European Commission however, explain it slightly differently as: "the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient."[35]

'Transitioning' and 'switching' are actions performed by physicians and describe a single transition of patients from a reference product to a biosimilar. The term 'substitution' refers to an action performed by pharmacists and is very different: "dispensing one medicine for another equivalent and interchangeable medicine at the pharmacy level without consulting the prescribing physician."[35]

The need to medically-switch patients is common practice and has a strong evidence base.[4,5,36] Non-medical switching involves changing stable patients either to different agents from the same class, or from a reference product to its biosimilar, or vice versa.[6] The motivation behind such switches can range from the potential for cost savings and procurement policies to patient preference.[7]

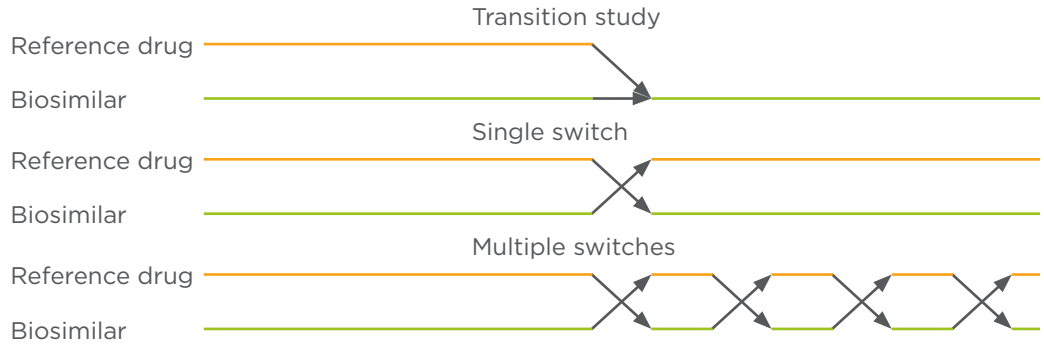


**Figure 3: Study designs: transition, substitution, and interchangeability.[39]**

Reference products currently available have been uniquely identified and differ in mechanism of action; all have undergone the same full clinical development pathways required for regulatory approval.[37,38] The number of biologics for the treatment of inflammatory and rheumatic diseases is expected to increase substantially in the near future, creating the clinical challenge of identifying the right drugs for patients at each stage of treatment.[39]

A review by Ebbers et al.[40] analysed data from 12,039 patients, switched between either reference products or biosimilars of human recombinant growth hormones, erythropoietins, and granulocyte colony-stimulating agents. The study concluded that there are limited clinical data investigating the effects of switching and transitioning to biologics, and many of the identified studies were not designed to identify switching-related adverse events.[40] There is a need for substantive data and adequate post-marketing surveillance regarding non-medical switching. Currently, according to these results, there is no indication that switching impacts therapy safety and efficacy.

A study of non-medical switching from infliximab to adalimumab in 36 inflammatory bowel disease patients with Crohn's disease reported that 47% of switched patients required dose optimisation and 28% required treatment interruption, compared with 16% and 2%, respectively, in the 'continue on infliximab' group. The results suggest that adherence to the first anti-TNF is recommended if patients are stable.[41]

The British Society for Rheumatology (BSR) advises against summarily switching all patients to biosimilars, recommending that switching should only be undertaken on a case-by-case basis until further data are available to support the approach.[42] The ACR concurs, believing that there are too many unknowns about biosimilars to ensure that switching will be a safe practice.[43] However, guidance from the British Society of Gastroenterology (BSG) states that there is sufficient evidence to recommend switching for stable patients or those in remission on Remicade® therapy to Remsira® or Inflectra® at the same dose and dose interval.[44]

There is increasing evidence regarding switching among reference products and biosimilars for several indications, including rheumatic diseases. However, the study designs between trials can vary widely, creating the need for robust data regarding switches and interchangeability to be generated.[45,46]

Repeated switching between biosimilar and reference product may increase immunogenicity.[47] The interchangeability of reference products and biosimilars needs to be demonstrated by repeated switches between the two. This would require randomised controlled trials that include at least two switches and appropriate control groups (Figure 3).[39] However, such scenarios do not reflect common practice, and rigorous clinical studies to address aspects of non-medical switching cannot be expected.[48]

Global post-marketing surveillance is needed to gain a better understanding of long-term efficacy and safety, as there could be limitations in pre-approval studies. Sufficient pharmacovigilance is needed to continually assess the risk-benefit profile of every drug and minimise the risks associated with their use.[49] Effective pharmacovigilance requires tracking, tracing, and analysis of specific products. However, the traceability of biologics and biosimilars poses novel challenges in pharmacovigilance. A clear naming system is needed, as well as robust systems to ensure

traceability through the pharmaceutical supply chain and efficient transfer of exposure information to pharmacovigilance data sources.[50,51]

In conclusion, both reference products and their biosimilars are important expansions of treatment options for rheumatic diseases. Switching between different biologics, and even between versions thereof, is an emerging field, which may impact on pharmacovigilance requirements, and highlights the need for further study and awareness. Pharmacovigilance overall is critical, and requires exact identifiers; it may enable adverse effects or any other possible drug-related problems in clinical practice to be detected, assessed, understood, and prevented.

## Question and Answer Session

If biologics are a mixture, why is there a fear of biosimilars working differently?

Dr Revers responded that contamination can be removed from biologic molecules, while it is a case of maintaining consistency in a product. He stated that the issue largely resides with the fact that comparisons were initially made between biosimilars and biologics, and the consistency needs to be maintained between them. This is particularly difficult for manufacturers when there are more than 30 entrants to the market. Dr Revers added that he is very open to biosimilars if they are tracked appropriately.

What is the difference between non-medical switching and interchangeability?

Prof Keystone clarified that the FDA definition of 'interchangeability' means patients can be switched from a reference product to a biosimilar and then switched again, back to the reference product, and it is the pharmacist that makes the decision. Prof Keystone noted that it is a very difficult definition to achieve, and studies of switching both ways are needed, adding that currently the FDA has not given any of the products interchangeability status.

How do you explain the difference in terms of anti-drug antibodies? There were definitely more anti-drug antibodies with etanercept, 13% versus the biosimilar.

Prof Keystone felt that this is not currently clear. He stated that there are a lot of suggestions that maybe it is bad to switch etanercept due to anti-drug antibodies and that others say it is a detectability issue. He concluded that the answer is not known.

Are the data presented on availability of Humira and its biosimilar from products approved in the European Union, USA, or other countries?

Dr Revers stated that he was not sure how to answer. One of the interesting stories about biosimilars that emerged in the symposium is that manufactures of originators are asked: 'How consistent are your products?', because if there are new companies making biosimilars, surely the manufacturers of the originators have been making changes to their product and therefore the product today is not the same as when it first launched. Examples have been seen that demonstrate the variability in products. Differences in etanercept have been noted between the USA and European Union, indicating changes from the originator product. Dr Revers commented on the imminent entrance of many biologics, and the need for each to be sufficiently tracked.

### Footnotes

(*) 10-year data has also been published.[22]

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# PRECISION MEDICINE: MAXIMISING TREATMENT BENEFIT FOR RHEUMATOID ARTHRITIS PATIENTS

## This symposium took place on 9th June 2016 as part of the European League Against Rheumatism (EULAR) Congress 2016 in London, UK


**Chairperson**

**Ernest Choy[1]**

**Speakers**

**Ernest Choy,[1] Eric Ruderman,[2] Cem Gabay,[3] Georg Schett[4]**

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## MEETING SUMMARY


This educational symposium was opened by Prof Ernest Choy, who introduced the concept of precision medicine and highlighted the importance of integrating current research with clinical experience to guide treatment decisions. He also highlighted the growing recognition of precision medicine within rheumatology. Prof Eric Ruderman then explored current medical views around the use of glucocorticoids (GCs) in rheumatoid arthritis (RA), revealing how uncertainty over the true risk/benefit ratio of these agents means that their impact as part of patient care must be further studied. Next, Prof Cem Gabay reviewed the evidence from clinical trials, registries, and real-world studies supporting biologic monotherapy as a treatment strategy in patients for whom methotrexate (MTX) is inappropriate. Prof Georg Schett then considered how current biomarker research might influence patient care in the future, especially with respect to assessing disease course and treatment responses in RA. Finally, Prof Choy presented a series of patient case studies, featuring practical issues faced by rheumatologists in the clinic, and drew upon the themes of the preceding presentations to highlight the value of a precision medicine approach to RA. Following closing remarks from Prof Choy, a lively discussion session enabled the audience to ask the expert panel about the wider clinical implications of their views.

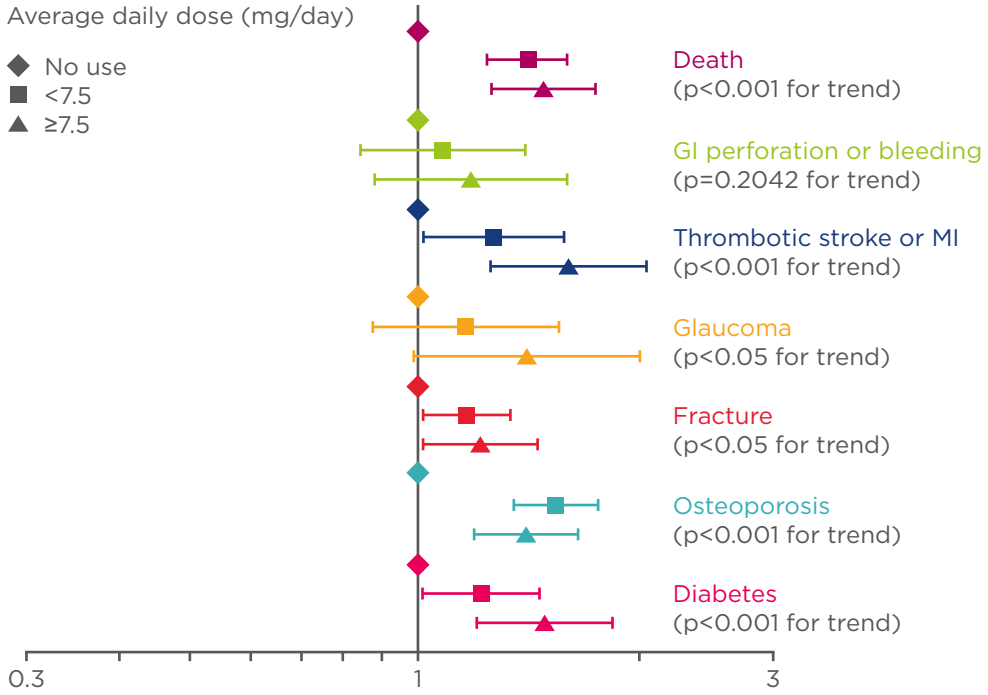


**Figure 1: Increased risk of serious adverse effects associated with glucocorticoid use in UK population-based study.[11]**

Forest plot displaying the adjusted odds ratio with 95% confidence intervals for the outcomes of interest with increasing average oral glucocorticoid use in patients with rheumatoid arthritis.

GI: gastrointestinal; MI: myocardial infarction.

## Welcome and Introduction

### Professor Ernest Choy

Precision medicine means providing the best available healthcare by identifying the needs and maximising the outcomes of individual patients. Recognition of precision medicine in the field of rheumatology is growing.[1,2] This approach not only integrates current research and clinical practice, but also requires close partnership and communication with the patient.

The current European League Against Rheumatism (EULAR) recommendations outline that remission or low disease activity should be the goals of treatment in every patient.[3] Yet to achieve these aims, a greater understanding of the immune parameters for therapeutic intervention is needed. In particular, novel insights concerning cytokines involved in RA pathogenesis, such as interleukin (IL)-6, would help to guide appropriate therapeutic strategies.[4,5] The pivotal role of IL-6 in RA[5] was explored in a video at the beginning of the session, which highlighted the importance of further research in this area (available to view here).

## Reviewing the Role of Glucocorticoids in Rheumatoid Arthritis Management

### Professor Eric Ruderman

GCs are frequently prescribed by rheumatologists as they are known to be powerful, fast-acting anti-inflammatory drugs.[6] Yet, despite their long history in medicine, their introduction predated the establishment of regulatory requirements for safety and efficacy[6] and so there is a lack of certain data for GCs that would be considered as essential requirements for therapies approved in RA today. Chronic GC use has been associated with numerous side effects, some of which are potentially life-threatening, and the incidence of adverse events is influenced by GC dosage.[6,7] A better understanding of the true risk/benefit ratio of GCs is needed to determine how best to use these agents.[6-8]

Although controlled trials for GCs have been conducted, the published reports reveal important limitations such as short study duration and differing endpoints, thus observational data are needed to supplement the findings.[9] Data from a UK primary care database have highlighted that around half of patients with RA received a

prescription for a GC at some point in their follow-up, illustrating that these agents are still widely used.[10] The same UK source has also revealed the potential downside of using GCs. Increasing oral GC cumulative and average daily doses were clearly associated with greater risks of various serious adverse events, namely, diabetes, osteoporosis, fractures, glaucoma, hypertension, thrombotic stroke or myocardial infarction, gastrointestinal perforation or bleeding, and death (Figure 1).[11]

The risk of serious infections in patients on long-term GC therapy is a particular concern, with higher risks being observed with increasing age, cumulative dose, and longer duration of treatment.[12] This heightened serious infection risk is even observed in RA patients achieving Disease Activity Score 28 (DAS28) remission, a fact which suggests that the serious infection risk with GCs is not confounded by disease activity.[13] Furthermore, increased serious infection risk was also observed in anti-tumour necrosis factor (anti-TNF)-treated RA patients receiving low doses of GCs.[14] As with serious infections, the risk of myocardial infarction is also influenced not only by the total GC dose, but also by the cumulative dose over time.[11] Importantly, GC use has been associated with significantly increased mortality risk in patients with RA and may abrogate some of the cardiovascular benefits that have been described with MTX therapy.[7]

The current EULAR research agenda has identified several GC therapy-related knowledge gaps and the uncertainty over long-term safety of GC therapy has also been reflected in national guidelines and recommendations for the management of RA.[3,15,16] Although specific guidance is lacking, the general theme that emerges is that GCs should be used sparingly and that they should be tapered whenever possible.[3,15,16] Emerging observational data show the GC-sparing potential of biologics which illustrates a way forward to improving management. One French study showed that the GC-sparing effects of anti-TNFs were apparent within 3 months of initiation,[17] while another showed the decreased use of GCs in some biologic-experienced patients from Europe and Canada who were taking abatacept.[18] Similarly, two French observational studies have demonstrated the GC-sparing effect of tocilizumab accompanied by a decrease in disease activity.[19,20] Additional studies, such as the SEMIRA randomised controlled trial, which will assess whether it is possible to safely taper and discontinue GCs while maintaining disease activity control with tocilizumab, should contribute further valuable information on the GC-sparing potential of biologics and GC-tapering approaches.[21]

Overall, while the beneficial effects of GCs have been well documented, it is notable that significant adverse events associated with use of these agents have also been frequently described.[6-8] It is not only rheumatologists who are concerned about the risk/benefit ratio of GCs but also patients.[8] Therefore, the impact of GC treatment as part of care should be taken into account to maximise treatment outcomes as part of a precision approach.

## Monotherapy in the Rheumatoid Arthritis Treatment Landscape

### Professor Cem Gabay

Biologic monotherapy is a treatment strategy in patients for whom MTX is inappropriate; real-world data from different national registries show that approximately a third of RA patients on biologics are on monotherapy.[22] The efficacy of MTX has been well characterised, and the current EULAR recommendations state that it should be part of the first treatment strategy in patients with active RA.[3] However, its use does present some patients with challenges, such as inadequate response and adverse events, as well as potential implications for their lifestyle.[23] This helps explain why some patients do not use MTX as prescribed, yet their rheumatologist may be under the impression they are fully adherent.[23] For example, Canadian healthcare claims data showed that 58% of patients prescribed biologic combination therapy with MTX did not collect their MTX prescription.[24] Such information highlights a disconnect between the rheumatologists' perceptions and the reality of patient MTX use.[23,24] Nevertheless, the reasons for this lack of adherence are multifactorial and need further exploration.[23,24]

The EULAR recommendations highlight that biologics should be combined with disease-modifying anti-rheumatic drugs (DMARDs), and that MTX is preferred.[3] If MTX treatment is inappropriate, tocilizumab monotherapy is recognised as a potential option;[3] this general approach for tocilizumab monotherapy is also recommended in a number of national guidelines.[15,16]

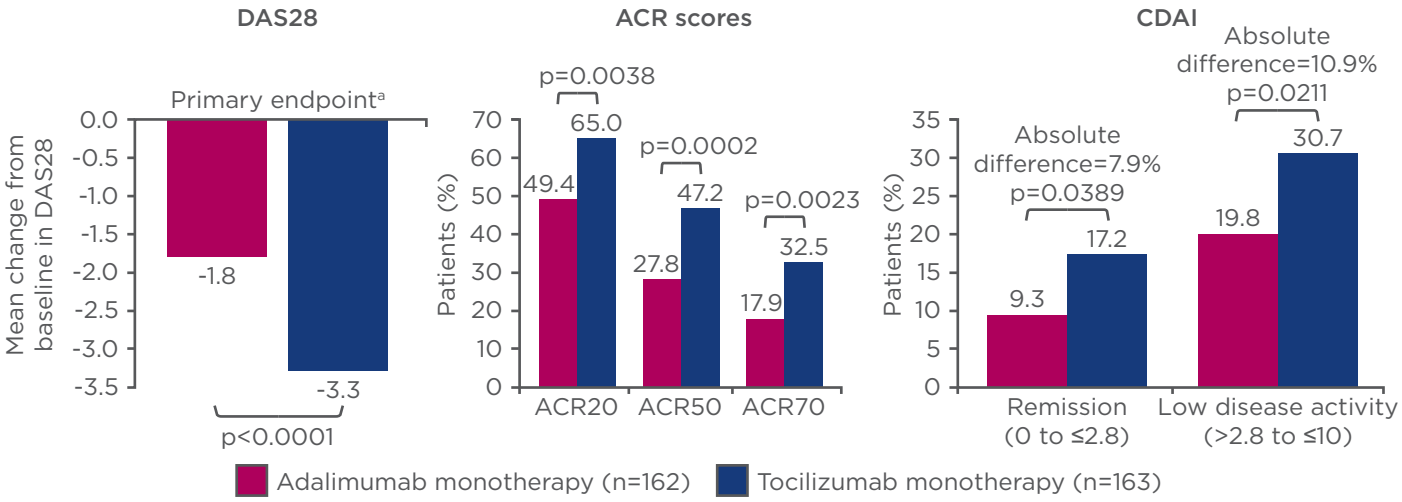


**Figure 2: Superior efficacy of tocilizumab monotherapy versus adalimumab monotherapy in the ADACTA trial.[25]**

[a]Adalimumab group: Baseline DAS28=6.8, Week 24 DAS28=5.0; Tocilizumab group: Baseline DAS28=6.7, Week 24 DAS28=3.4.

ADACTA head-to-head 24-week study of tocilizumab monotherapy vs. adalimumab monotherapy in patients who were intolerant to MTX or inappropriate for continued MTX.

DAS28: disease activity score 28; ACR: American College of Rheumatology; CDAI: clinical disease activity index; MTX: methotrexate.

*Adapted from Gabay C et al.[25]*

These conclusions for tocilizumab were reinforced by the results of the head-to-head ADACTA trial, where tocilizumab as monotherapy was shown to be statistically superior to adalimumab monotherapy in terms of DAS28 response, American College of Rheumatology (ACR) responses, and Clinical Disease Activity Index (CDAI) response (Figure 2).[25] The ACT-RAY study has also extended understanding of tocilizumab monotherapy;[26,27] the 24- and 52-week data compared an add-on strategy (tocilizumab in combination with MTX) with a switch strategy (tocilizumab with placebo) in patients with an inadequate response to MTX.[26,27] ACT-RAY demonstrated that for patients who cannot be treated with MTX, a switch to tocilizumab monotherapy is an option that may provide a robust level of disease control and radiographic benefits but does not result in any additional safety concerns.[26,27]

With anti-TNFs the comparative clinical results between combination and monotherapy are different from those reported for tocilizumab. Data from the PREMIER trial showed that adalimumab and MTX combination therapy was superior to both MTX and adalimumab monotherapy in all outcomes measured.[28] Similarly, the results of the TEMPO trial showed that etanercept and MTX combination therapy resulted in significantly greater improvement in DAS and in more patients achieving disease remission than either MTX or etanercept monotherapy.[29]

Other analyses suggest distinct characteristics of tocilizumab as monotherapy compared with other biologics. A network meta-analysis of trial findings found that the Health Assessment Questionnaire Disability Index (HAQ-DI) improvements with anti-TNFs, abatacept, and tocilizumab in combination with MTX were comparable.[30] However, while the HAQ-DI improvements with tocilizumab as monotherapy were similar to that of tocilizumab in combination with MTX, anti-TNFs as monotherapy appeared to be less efficacious than anti-TNFs in combination with MTX.[30]

The monotherapy findings for tocilizumab have also been investigated in broader populations than in clinical trials. ACT-SURE, an open-label safety and effectiveness study conducted in 25 countries, found that tocilizumab had a comparable safety profile, and was similarly effective, when used as monotherapy or in combination with DMARDs.[31] Data from the Pan-European registry TOCERRA also support the

effectiveness of tocilizumab monotherapy.[32] CDAI decreased rapidly after the start of tocilizumab, regardless of whether it was used as monotherapy or in combination with DMARDs.[32] For CDAI remission, there was no significant difference between the various tocilizumab treatment groups (with or without concomitant DMARDs) at any of the time points.[32] Importantly, the ACT-UP study, a multinational, observational study, found that tocilizumab was well tolerated as monotherapy in routine clinical practice, with comparable safety results to tocilizumab in combination with MTX.[33] The impact of tocilizumab monotherapy on patient-reported outcomes is also emerging from patient registry data analysis. The US CORRONA registry data showed improvements at 1 year with tocilizumab monotherapy for all reported measures, regardless of prior anti-TNF history.[34]

There remains a gap in our understanding of how to predict patient response to different biologics, particularly when given as monotherapy. Studies have been undertaken to explore biomarkers, but validation of the results is essential. For example, variable findings have been reported for CD11c with anti-TNF monotherapy and so larger biologic monotherapy biomarker studies are required.[35]

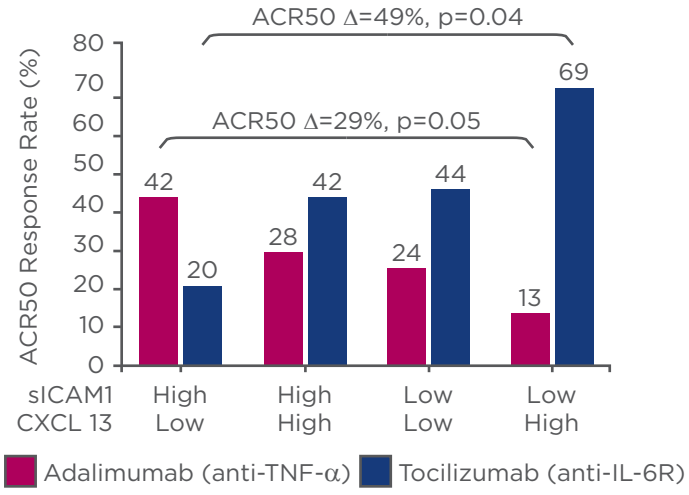


**Figure 3: Lymphoid (CXCL13) and myeloid (sICAM1) serum biomarkers define rheumatoid arthritis patient subgroups with differential clinical response to adalimumab compared with tocilizumab in the ADACTA trial.[36]**

ACR: American College of Rheumatology; CXC13: C-X-C motif chemokine 13; sICAM1: soluble intercellular adhesion molecule 1; anti-TNF-α: anti-tumour necrosis factor alpha; anti-IL-6R: anti-interleukin 6 receptor; RA: rheumatoid arthritis.

More promising biomarker results have been generated in a sub-study of the ADACTA head-to-head biologic monotherapy trial, where lymphoid (CXC motif chemokine 13 [CXC13]) and myeloid (soluble intercellular adhesion molecule 1 [sICAM1]) serum biomarkers defined RA patient subgroups with differential clinical response to adalimumab and tocilizumab monotherapy (Figure 3).[36] A higher ratio in favour of CXCL13 was associated with an increased likelihood of response to tocilizumab monotherapy. In contrast, a higher ratio favouring ICAM-1 was associated with an increased likelihood of response to adalimumab monotherapy.[36] These represent the first biomarker findings indicating differential clinical response to anti-TNF and anti-IL-6 receptor agents used as monotherapy.[36] Validation of these initial biomarker findings will help predict the response to biologic monotherapy and so enable the selection of the right drug for the right patient.

## Can Biomarkers Help Guide Biologic Treatment Approaches?

### Professor Georg Schett

Although advances are being made in the field of RA, biomarker research has lagged behind in areas such as oncology, a fact which necessitates more efforts in research to drive progress for the future.[37,38]

A biomarker is an objectively measured indicator of normal biological or pathogenic processes or of response to treatment.[38] Biomarkers are identified by preclinical studies and clinical assays are then developed, which must be validated retrospectively and prospectively before they are accepted in the clinic.[38] A biomarker is fundamentally different to an outcome. A biomarker is a process-centred instrument and has no meaning to the patient. In contrast, an outcome is a patient-centred instrument and has immediate meaning to the patient.[37] The biomarker C-reactive protein (CRP) will not have relevance for the patient, but the outcome of RA will be evident to the patient.

Prognostic biomarkers predict the course of a disease irrespective of treatment, whereas predictive biomarkers predict treatment response.[38] Elevated CRP is an example of prognostication of relevance to rheumatologists as it is independently linked to risk of vascular and non-vascular deaths.[39] Hard endpoints require a long period of follow-up

before they become apparent; therefore, surrogate outcomes are useful in clinical practice. Surrogate outcomes or effects on surrogate outcomes should correlate with clinical outcomes or effects on clinical outcomes, respectively.[38]

In RA, structural damage is a surrogate outcome for death and several prognostic biomarkers for structural damage have been identified. Anti-citrullinated protein antibodies (ACPA), rheumatoid factor (RF), CRP, calprotectin, matrix metalloproteinase-3, 14-3-3η, receptor activator of nuclear factor kappa B ligand (RANKL) and osteoprotegerin, C-terminal cross linking of Type-I and Type-II, have all been identified as prognostic biomarkers for poor structural outcomes in RA.[40-43]

It is now possible not only to predict a surrogate outcome, but also to predict a clinical outcome such as the onset of RA. This will be important for the future of precision medicine as it will help define patients early. A promising approach is combined analysis of prognosticators, such as autoantibodies which are known to precede the onset of RA. It has been shown that more patients with a combination of RF, ACPA, and 14-3-3η autoantibodies progress than those with only one of these biomarkers.[40,41]

A more difficult field is the prediction of treatment response. Analogous to the field of oncology, there is now an appreciation that RA is a heterogeneous disease, varying between patients and driven by different immunopathological processes and that subgroups of patients can be identified so that they can be stratified to individual treatments.[44] For example, RF and anti-cyclic citrullinated peptide (anti-CCP) seropositivity are predictive of better treatment responses to rituximab and to abatacept in biologic-naïve RA patients at 6 months.[45-47] Yet, a similar association between anti-CCP seropositivity and treatment response has not been observed for anti-TNF therapies, and may be indicative that autoantibody development is not intimately linked to the production of TNF.[48]

The relationship between the mechanism of action of a biologic drug and biomarkers is clearly complex, and prior assumptions of an interaction may prove to be invalid. With tocilizumab for example, baseline CRP and IL-6 levels are not predictive of clinical outcomes following treatment.[49] Multi-biomarker disease activity scores, which are based on the serum levels of 12 different proteins, are also not predictive of response to tocilizumab treatment.[50] In the future it will be important to appreciate that there are different biomarkers showing immune activation; biomarkers such as CRP, fibrinogen, and serum amyloid A have been well described with respect to the acute phase response, but other processes are being investigated. For example, as shown in the biomarker sub-study of the ADACTA trial, CXCL13 appears important in innate/adaptive immune activation.[36]

A challenging but central goal is to find predictors for treatment response in order to tailor treatment for individual subsets of RA. The ongoing Phase III STRAP (Stratification of Biologic Therapies for RA by Pathobiology) study, conducted by the MATURA industry–academia consortium, is expected to generate important data in this regard.[51] The three biologics that will be studied in the STRAP study are rituximab, etanercept, and tocilizumab.[51] Through the use of biopsies the investigators aim to subtype patients to better understand the underlying disease pathways.[51] The outcomes of STRAP are eagerly awaited. If predictors of response to drugs can be reliably identified, then patients with RA would be able to receive the drug that they are most likely to respond to earlier than is possible at present.

## Innovating Future Treatment Approaches in Rheumatoid Arthritis Through Previous Clinical Experiences

### Professor Ernest Choy

The insights from clinical practice are essential for the effective delivery of precision medicine.

In case study 1, a 58-year-old female patient initiated treatment with MTX in 2012, which improved her condition. She was given adalimumab with MTX in 2014 after displaying signs of worsening disease activity but she still experienced disease progression. The general view of the audience was that a switch to an alternative biologic agent would be an appropriate future clinical approach for such a patient. The discussion highlighted the importance of considering adherence and working in partnership with the patient. This theme was then further explored by looking at observational data which confirmed that patient adherence to medication is suboptimal, but that

the reasons behind the phenomenon are complex and multifaceted.[52,53]

In case study 2, a 52-year-old male patient initiated treatment with MTX in 2011 but this had limited effect. In 2013, he was switched to etanercept plus MTX and his symptoms improved. In 2016, prednisone was added to his treatment regimen but he complained of fatigue, mood changes, insomnia, and weight gain despite disease activity being moderately controlled. The subsequent discussion with the audience centred on the uncertainty regarding the risk/benefit profile of GCs, and how this needed to be factored into clinical decision-making to ensure that the patient received the optimal treatment approach. From a practical perspective, this necessitates consideration of the patient's age, intended GC treatment duration and dose, as well as comorbidities and co-medications.[8-12]

In case study 3, a 60-year-old female patient initiated treatment with MTX, hydroxychloroquine, and intramuscular GC injection in June 2015. She was switched to subcutaneous MTX following a dose increase that resulted in nausea and loss of appetite. After failing to attend several appointments, she experienced a flare of her RA and, when brought to the clinic by her sister, admitted to her physician that she had stopped all treatment due to hair thinning. The audience recognised this case as highlighting the need for better dialogue with patients[3] and the fact that partnership was essential for the delivery of precision medicine. Patients may have different viewpoints on healthcare from those of physicians and so a shared approach may lead to improvements in health outcomes, coping behaviour, adherence, and satisfaction with care.[54,55]

## SUMMARY

An increasing focus on precision medicine in RA will drive better patient outcomes. As part of this, the impact of GCs, which are commonly used agents, must be further studied due to the uncertainty surrounding the true risk/benefit profile of these drugs. Biologic monotherapy is a valuable treatment strategy in patients with RA for whom MTX treatment is inappropriate and data from registry and real-world data corroborates what has been seen in clinical trials. Looking to the future of precision medicine in RA, continuing research into predictive biomarkers for treatment response will enable better care to be delivered to patients earlier in the disease process. Precision medicine relies on the close integration of current research and clinical practice to better guide decision-making and ultimately ensure treatment benefits for RA patients are maximised.

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# THINK RHEUMATOID ARTHRITIS: CAUSES, CONSEQUENCES, AND MANAGEMENT

## This satellite symposium took place on 9th June 2016, as a part of the European League Against Rheumatism (EULAR) 17th annual congress in London, UK


**Chairpersons**

**Josef Smolen,[1] Costantino Pitzalis[2]**

**Speakers**

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## MEETING SUMMARY


Prof Josef Smolen opened the symposium and briefly described the aims of the meeting. Co-host Prof Constantino Pitzalis first discussed the pathophysiology of rheumatoid arthritis (RA), identifying the pro-inflammatory cytokines involved and explaining why specific drugs only work in certain conditions. Prof Simon Jones followed with a discussion on comorbidities and adverse events associated with interleukin (IL)-6 intervention in rheumatic disease. Dr Frank McKenna presented on the psychological impact of RA, including mood changes and development of depressive disorders, and Prof Smolen described the upcoming therapeutic approaches for the condition while also comparing and contrasting existing treatment options. The symposium concluded with a question and answer session.


## Pathophysiology of Rheumatoid Arthritis

### Professor Costantino Pitzalis

RA is a chronic inflammatory condition characterised by proliferative synovitis, which normally involves angiogenesis, infiltration of lympho-monocyte cells, and production of pro-inflammatory cytokines, and leads to chronic destruction of the joint. Because the disease is heterogeneous, it is important to understand what accelerates destruction of the joints in some patients and not others to ensure that appropriate treatment can be directed at those patients.

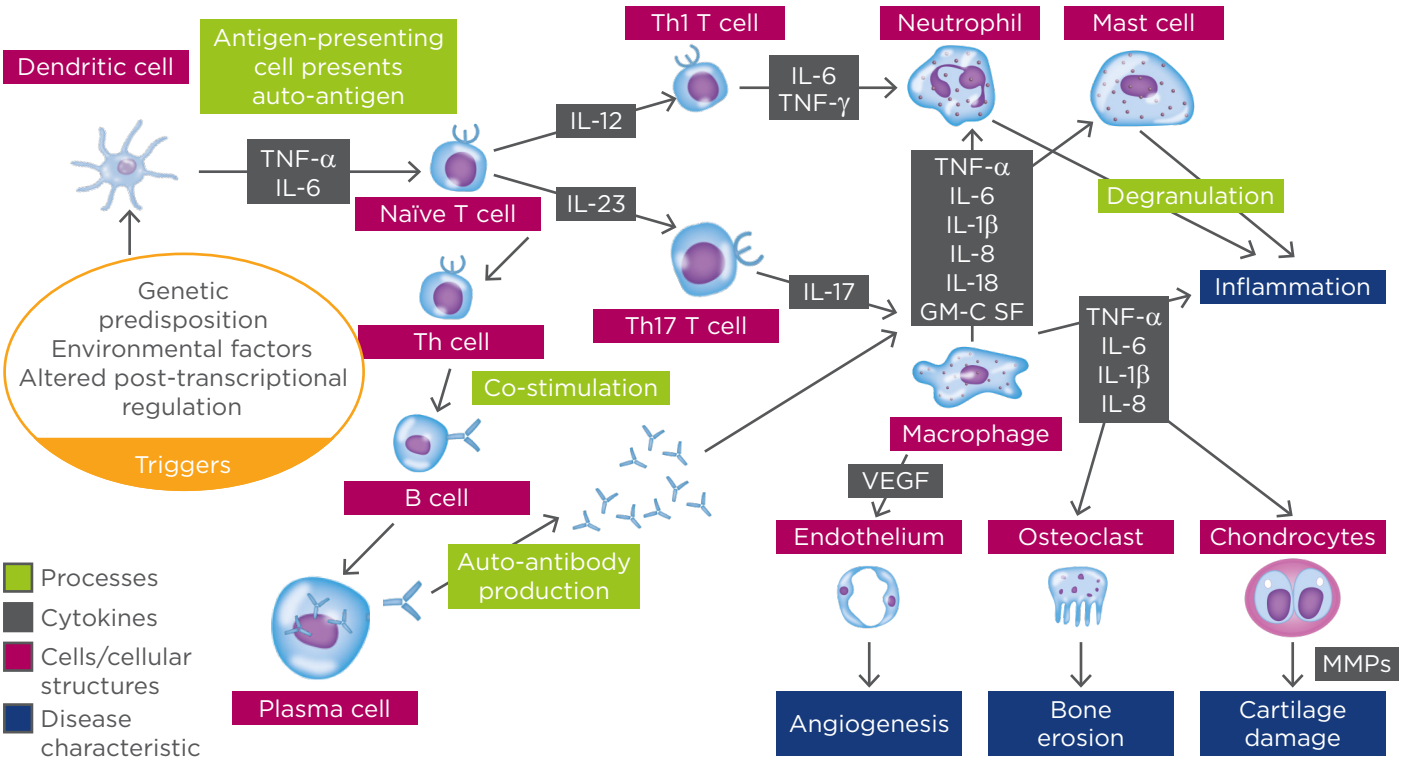


**Figure 1: Pathophysiology of rheumatoid arthritis.**[3,5,7-10]
GM-CSF: granulocyte macrophage colony-stimulating factor; IFN: interferon; IL: interleukin; MMPs: matrix metalloproteinases; Th: T helper; TNF: tumour necrosis factor; VEGF: vascular endothelial growth factor.
*Adapted from Smolen JS et al.,[7] McInnes IB and Schett G,[8] Choy E,[5] Furst DE and Emery P,[9] Smolen JS et al.,[3] Komatsu N and Takayanagi H.[10]*

The disease can be divided into pre-clinical and clinical phases. In the pre-clinical phase, the development of RA involves a complex interplay between genotype, environmental triggers, and chance. Genetic predisposition to RA and encounters with some environmental insults, such as an infection, can lead to immunological dysfunction and initiate the production of auto-antibodies, such as anti-cyclic citrullinated peptide (anti-CCP) or rheumatoid factor antibodies. Auto-antibodies can be silent for up to 15 years, thus, patients may have systemic autoimmunity but show no symptoms. Some patients may then progress to an aggressive form of the disease, while others may have a mild form of RA. At present, there is no cure for RA, which is why identifying immune-dominant initiating factors, understanding what leads to the diverse disease evolution in some patients and not others, and why some patients respond to particular treatment while others do not, could be crucial to effectively stopping joint damage with first-line treatment.

Genome-wide analyses identify risk alleles associated with immune signalling involved in RA. These include nuclear factor-κB-dependent signalling and T cell stimulation, activation, and functional differentiation alleles. Environmental factors that may trigger the disease include infection (Epstein–Barr virus, parvovirus, cytomegalovirus, *Escherichia coli*, or Proteus bacterial species), trauma, smoking, and gastrointestinal microbiome. Another trigger is altered post-transcriptional regulation: all patients with RA have dysregulated citrullination of peptides which means proteins are no longer recognised as 'self' as they are secreted, leading to auto-antibody production/autoimmunity.[1] Although all these triggers are known, it is unclear which one(s) drive the disease.

Loss of tolerance to certain proteins leads to aberrant immune response to 'self' proteins in the regional lymph nodes and secondary lymphoid organs: antigen-presenting dendritic cells present 'self' antigens to specific major histocompatibility complex II molecules, driving the production of pro-inflammatory cytokines, activating T cells[2,3] which in turn activate B cells to produce auto-antibodies,[4] a characteristic feature of RA.

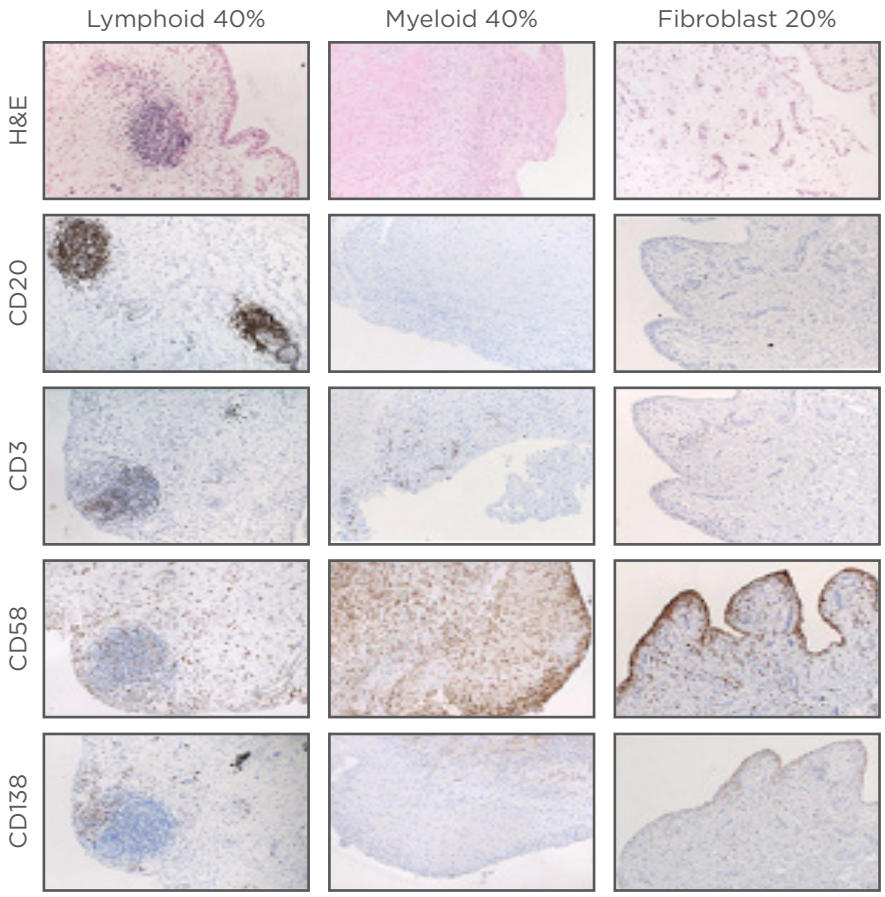


**Figure 2: Identification of tissue pathotypes (digital pathology).**
H&E: haemotoxylin and eosin stain.

Auto-antibodies can form larger immune complexes that can further stimulate the production of pro-inflammatory cytokines, including tumour necrosis factor (TNF)-α, through complement and Fc-receptor activation.[5] The production of anti-CCP antibodies is a key event in RA and it has been shown that the titre of the anti-CCP antibody rises dramatically before the development of clinically apparent disease.[6] Low titres of these antibodies may be present in patients with RA and then suddenly rise rapidly and trigger RA. Auto-antibodies most likely bind citrullinated antigens within the joint itself, forming new complexes that initiate an inflammatory escalation.[6] A non-specific infection or trauma, for example, may lead to the arrival of dendritic cells or neutrophils into the joint presenting citrullinated auto-antigens. Since the patient has systemic autoimmunity, the auto-antibodies bind these antigens locally. Further immunological response then progresses to pro-inflammatory cytokine production via T cell and macrophage activation, as well as differentiation of some T helper cells that induce B cells to produce more auto-antibodies locally. In the acute phase response, IL-6 has the greatest effect on acute-phase protein levels leading to synthesis ofproteins such as fibrinogen, C-reactive protein (CRP), hepcidin, and serum amyloid A.[5] The response further leads to the activation of endothelial cells and subsequently angiogenesis. Moreover, activation of osteoclasts results in bone erosion, while inhibition of chondrocyte metabolism causes cartilage damage (Figure 1).[3,5,7-10]

Various drugs target different cytokines (e.g. TNF-α and IL-6 blockers), yet the response pattern is the same for the treated patients: around 60% of patients achieve a 20% improvement in symptoms, 40% of patients experience a 50% improvement, and 20% of patients show 70% improvement in symptoms after treatment.[11] This may indicate that the population of patients treated is very resistant and requires new medication, or that alternative mechanisms are at work. Adherence to treatment may be an issue, as well as formation of anti-drug antibodies.

Taking a biopsy of the diseased tissue would provide a molecular and histological

characterisation that could identify the pathway driving the disease in specific patients. To date, three different synovial pathotypes have been identified: a lymphoid pathotype in which there are many B cells, which form large aggregates in disease tissue of patients never treated with disease-modifying anti-rheumatic drugs (DMARDs); a myeloid pathotype characterised by high inflammation and virtually no B cells; and a fibroid pathotype that involves very little inflammatory infiltrate (Figure 2),[12] driven by cell types other than immunological cells.[13]

Biopsy is a complex and invasive procedure for the patient, so it is important to also evaluate peripheral blood for biomarkers. A study in the USA has shown that the defining circulating biomarkers are soluble intercellular adhesion molecule 1 (ICAM1) and chemokine (C-X-C motif) ligand 13 (CXCL13); these are expressed at highest levels in the myeloid and lymphoid phenotypes, respectively. In a head-to-head comparison of adalimumab versus tocilizumab, nearly 70% of patients with high levels of CXCL13 and low levels of ICAM1 treated with tocilizumab achieved a 50% improvement in the condition.[13]

## Comorbidities and Adverse Events Associated with Interleukin-6 Intervention in Rheumatic Disease

### Professor Simon Jones

Of the number of drugs that target inflammatory cytokines, either directly or through their signalling receptors, each has a unique mode of action and individual pharmacodynamic properties that impact the way the drug works within a clinical setting. These drugs are very effective at targeting inflammation, thus also possibly affecting host defence, behaviour, and wellbeing.

In inflammatory arthritis, IL-6 is a primary driver of inflammation. Early studies have shown that mice deficient in IL-6 and challenged to become arthritic, were actually resistant to the pathology. Other evidence from when the anti-IL-6R receptor blocking monoclonal antibody tocilizumab was introduced has shown that IL-6 is a major component both in the regulation of inflammatory outcomes (acute phase response) and the immune activation processes. IL-6 is fundamentally linked with the control of cell survival and apoptotic mechanisms. It is also heavily associated with the differentiation of T cells, and has the ability to promote proliferation of certain cell types such as B cells.[14,15]

Currently, there are a number of different drugs targeting IL-6, although only tocilizumab is approved for the treatment of RA. These include very specific anti-IL-6 blockers and anti-IL-6R blockers, and less selective Janus kinase (JAK) inhibitors, soluble IL-6 receptor (sIL-6R) blockers, and signal transducer and activator of transcription (STAT) 3 blockers. These drugs affect downstream events such as transcription factors and signalling pathways, which are regulated as a consequence of engagement of IL-6 with its receptor complex.[14,15]

While IL-6 is a primary driver of RA outcomes, it is a wider acting cytokine that plays a role in adaptive and innate immunity. Under normal homeostasis, IL-6 is also involved in physiological responses. It is controlled partly by circadian rhythms, regulating glucose metabolism, lipid and iron transport, bone turnover, appetite, neuropsychological behaviour, and other mechanisms.[14,15] Therefore, targeting IL-6 pathways not only targets its ability to control inflammation, but also much more systemic processes in the body. For example, intervention with tocilizumab shows interference with normal homeostasis observed through serum lipid changes. In patients with active RA, systemic CRP levels are elevated as part of the acute response, while there is a decrease in levels of triglycerides and cholesterol. When this decrease is controlled by biologic intervention (such as tocilizumab), CRP and serum amyloid A levels normalise, but an increase in circulating lipids is observed.[16]

There are two modes of IL-6 signalling that are activated in the body as part of the immune response: classical IL-6 receptor signalling and IL-6 trans-signalling. In classical signalling, released IL-6 binds to a membrane receptor which consists of an α-chain IL-6 receptor (non-signalling by nature). It couples with a second β-subunit, glycoprotein 130 (gp130), which elicits the signal. The IL-6 receptor is confined to subsets of leukocytes, hepatocytes, and epithelial cells. However, the gp130 molecule is more highly expressed and is found on every cell type in the body. It is also known that IL-6 receptor (α-chain) is released into circulation at about 25–35 ng/mL and has the capacity to bind IL-6. This heterodimeric complex can then activate cell types that express gp130 on their cell surface,

broadening the repertoire of cells that become responsive to IL-6.[14,17] In terms of RA, structural cells within the joint primarily express gp130 but lack the IL-6R (found on inflammatory cells arriving at the site of inflammation) on their cell surface. sIL-6R/IL-6 complexes can then activate gp130 (trans-signalling). There is also a form of soluble gp130 (200–400 ng/mL) which can only bind sIL-6R/IL-6 complexes, thus acting as a natural antagonist in this particular system. In murine models of RA, when soluble gp130 is added to wild-type mice, disease activity is inhibited.[18-20]

While it may appear that trans-signalling plays a greater role in inflammation and classical signalling controls homeostatic mechanisms, the roles may be reversed as well (e.g. acute response in classical mode, and sleep and haematopoiesis control via the trans-signalling pathway).[14,15] One example of this dual nature is the role of IL-6, acting through its receptor, in controlling activities in the liver, such as glycogen consumption and regeneration. Under the control of IL-6 or IL-R blockade, there is an effect on iron transport linking the blockade to anaemia. Liver enzymes (aspartate aminotransferase/alanine transaminase) are also elevated in some patients, indicating liver damage; adding IL-6 to some experimental liver models shows that animals can actually be protected from liver damage with this wide-acting cytokine.[21,22] Studies of gastric tumours showed that any impact that distorts the control of IL-6 signalling is likely to influence homeostatic control of the regenerative process within the gut and lead to a loss of mucosal integrity (diverticulitis), gastric perforation, and other complications currently linked with tocilizumab and IL-6 intervention. Studies show that IL-6 plays an important role in controlling barrier maintenance (similarly to controlling infections).[23-25] Recurrent episodes of infection are important for driving the IL-6 involvement in steering the adaptive immunity, promoting or enhancing antimicrobial defence. At the same time, the effect may be detrimental and drive tissue injury and damage.

## The Psychological Impact of Rheumatic Disease

### Doctor Frank McKenna

The most commonly observed comorbidity in RA patients is depression. A study of almost 4,000 patients across Europe has shown a 15% prevalence in this psychological condition.[26] A meta-analysis by Matcham et al.[27] demonstrated that in a group of patients with a score of >11 in the Hospital Anxiety and Depression Scale (HADS), 15% of patients with RA were also depressed. However, with the group of patients that scored HADS >8, about one-third had some psychological aspect to their illness.[27]

Depression appears to be a similar risk factor for mortality as respiratory disease and only slightly less than cardiovascular disease or malignancy.[28] A study from India showed a positive correlation of about 0.45 between the Disease Activity Score 28 (DAS28) in patients with RA and severity of depression, indicating a moderate linear relationship between the two conditions.[29] The relationship was also shown through disability indices such as the Health Assessment Questionnaire (HAQ).[30] Interestingly, sleep disturbances in RA patients appear to reduce the pain threshold. A study of nine healthy volunteers deprived of sleep over a 6-day period showed changes in their pain threshold, particularly when limiting their slow wave (deep) sleep.[31] In just over 100 patients with moderate or active RA, all on methotrexate (MTX), there was a close correlation between the visual analogue scale of pain and the Pittsburgh Sleep Quality Index (r=0.65). A similar correlation was also shown between sleep deprivation or disturbance and fatigue in RA (r=0.63).[32] A study by Nicassio et al.[33] demonstrated how pain, depression, and also income contribute to sleep disturbance in RA. Given that many people with RA lose their work due to the disease, lower or no income further exacerbates the psychological condition of these patients.[33]

In patients with fibromyalgia, there was a likely correlation between arthritic pain, depression and anxiety, and sleep quality. Patients with fibromyalgia have many more psychological problems. They often sleep poorly and feel sleepy when awake, which also relates to patients with RA who wake with pain. In RA patients who already have depression and anxiety, their sleep quality relates to them having disturbed sleep, which is not the case for patients with fibromyalgia. The latter perceive sleep quality and sleepiness differently, and sleepiness is associated with other factors, some of which relate to their mood, particularly due to reduction in the slow-wave and rapid eye movement sleep stages. Patients with fibromyalgia do not stay in the stable sleep stage,[34] may have a high DAS28 even though they may have no

inflammatory disease, and have no tenderness in their joints, like in RA, but are tender everywhere.[35]

About 15% of RA patients, however, have secondary fibromyalgia or fibromyalgic RA (FRA). Compared with patients with RA only, patients with FRA experience more insomnia, mood disturbance, diffuse pain, and more tender joints, and thus show higher DAS scores.[36] Patients with FRA are often treated with more biologics and show less erosion and rheumatoid factor.[37] In the USA, a multi-biomarker disease activity (MBDA) score has been developed that contains 12 different factors.[38] MBDA score correlates strongly with levels of CRP and swollen joints.[39] Patients with FRA score higher MBDA and receive more treatment. Ultrasound data for these patients account not for the inflammatory markers, but for the amount of disease activity, which is greater in FRA.[40] Another study by Pollard et al.[41] showed that FRA affects 12–17% of RA outpatients and results in worse functional outcomes, but DAS28 scores over-interpret active disease in FRA.[41]

## Upcoming Therapeutic Approaches in Rheumatoid Arthritis

### Professor Josef Smolen

Currently, the American College of Rheumatology 70% improvement criteria (ACR70) rates are similar between different biologics treating RA. For all agents (including MTX, abatacept, golimumab, tocilizumab, and rituximab), with increasing drug experience there is a decreased response.[42] ACR70 rates were achieved in 30–45% of MTX-naïve patients, in 20% of MTX-experienced, and finally in 10% of anti-TNF-experienced patients. After treatment with MTX and three biological agents, about 50% of patients still showed insufficient response. Patients who did not respond to anti-TNFs displayed 10–12% response to all other biological agents.

While there are only two drugs, abatacept and rituximab, for T cell and B cell directed mode of action, respectively, there are five compounds (infliximab, etanercept, adalimumab, certolizumab, and golimumab) and three European Medicines Agency (EMA)-approved biosimilar TNF inhibitors (including infliximab [CT-P13]) for the treatment of RA. For IL-6 inhibition, there is only one drug available on the market, tocilizumab. There is also one IL-1 inhibitor, anakinra, which does not appear to be efficacious.

A new human monoclonal antibody to IL-6, sirukumab, has been investigated in a multicentre, randomised, double-blind, placebo-controlled, parallel-group study that will last 104 weeks with a 16-week follow-up. More than 1,600 patients with active RA (of at least 8 years duration) despite DMARD therapy, have been randomised (1:1:1) to sirukumab 100 mg once every 2 weeks (q2w), 50 mg once every 4 weeks (q4w), and placebo.

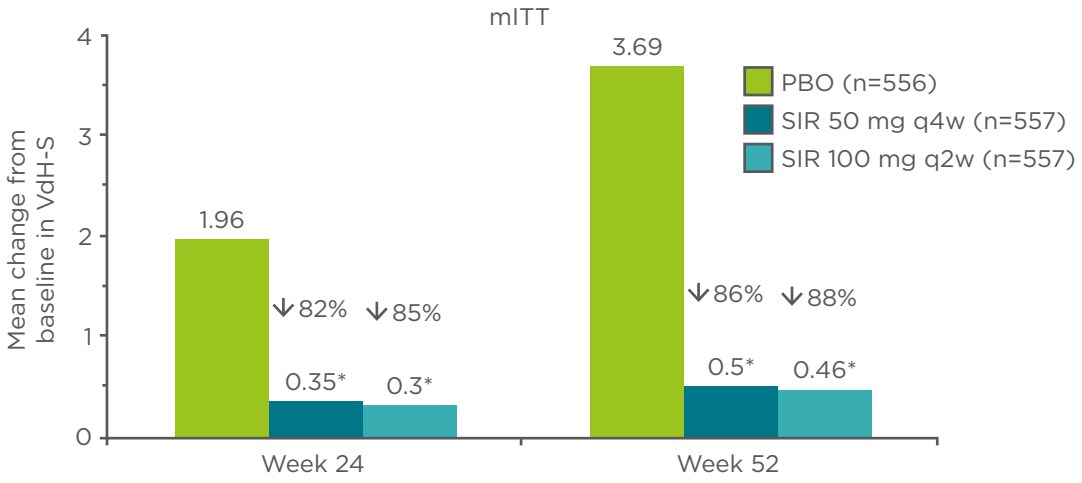


**Figure 3: Radiographic data.**
*p<0.001 versus placebo based on Van Der Waerden analysis of variance.
Based on imputed values by EE rules and then missing data rules.
VdH-S: Van der Heide/Sharp; mITT: modified intention-to-treat; q4w: once every 4 weeks; q2w: once every 2 weeks; EE: early escape; PBO: placebo; SIR: sirukumab.

At baseline, patients had high CRP levels, more than 80% were auto-antibody positive with a HAQ score of 1.5–1.6, and DAS28-CRP scores of around 5.9. This was a population of patients with severe torn joint damage and a high propensity to develop progression of joint damage.[43] A dramatic and fast reduction in radiographic progression was observed after 6 months and sustained through 1 year of treatment. Around an 88% reduction was observed in the 100 mg q2w group at Week 52 (Figure 3).[43]

In comparison, in the LITHE study of tocilizumab (this is not a head-to-head comparison and scores are also different), 70–74% inhibition of progression of joint damage was observed over 1 year.[44] In the sirukumab study, almost 60% of patients achieved American College of Rheumatology 20% improvement criteria at Week 16 and maintained the response over a year. American College of Rheumatology 50% improvement criteria results were similar to those in the LITHE study, with 30–33% of patients achieving the response (versus 12% on placebo). In terms of remission rates (measured by the Clinical Disease Activity Index [CDAI]), a significant difference was observed between sirukumab and placebo: 3-times as many patients on the study drug achieved remission. The same pattern was observed for CDAI in low disease activity. Changes in HAQ scores were also significant compared with placebo ($p \leq 0.001$), while the mean change in physical and mental components of the short-form 36 questionnaire was more than twice as much in the treatment group as in the placebo arm.[43] Fatigue was also significantly improved in treated patients compared with those on placebo ($p<0.001$).[45] IL-6 affects fatigue and mood in RA by influencing the hypothalamic pituitary adrenal axis, explaining why when a patient is infected and/or experiencing inflammation, they feel more tired.[46]

In terms of safety, 3.1% of patients on placebo, and 2.9% (50 mg) and 4.7% (100 mg) of patients treated with sirukumab experienced more than one serious adverse event at 18 weeks. The rates of serious infections were 2.6% (placebo), 4.6% (50 mg), and 3.8% (100 mg) per 100 patient-years. The rate of cardiovascular events was higher in the 50 mg arm but similar between the placebo and 100 mg groups at 52 weeks. It is unclear whether the different results for the two sirukumab doses were due to therapy or a chance occurrence.[43]

Overall, in DMARD-inadequate responders, sirukumab 50 mg q4w and 100 mg q2w reduced signs and symptoms of RA, inhibited radiographic progression, and improved health-related quality of life. Both co-primary endpoints and all major secondary endpoints were met, with both sirukumab doses showing statistically significant improvements compared with placebo.

In summary, RA is a heterogeneous disease that would benefit from stratifying patients based on pathotype and blood biomarkers allowing for more targeted and efficacious treatment. The mode of action of a particular drug has its benefits and side effects, and it is important to understand why a drug displays many specific characteristics in various processes, which are sometimes considered comorbidities or adverse events. There is increased morbidity and mortality in patients with RA who have psychological symptoms related to sleep, depression, fatigue, and pain, complicating disease assessment further. A new anti-IL-6 monoclonal antibody drug, sirukumab, showed promising efficacy and safety profiles, consistent with the known profile of existing anti-IL-6 treatment for RA.

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# NATURALLY OCCURRING LUBRICANTS TO MAINTAIN JOINT HOMEOSTASIS

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Cartilage surfaces sliding past each other in the major joints (such as hips and knees) exhibit extremely low levels of friction under physiologically high pressure, a lubricity which is essential for their healthy performance. Our objective is to obtain a detailed molecular-level understanding of this, which could benefit treatments of osteoarthritis (OA), as well as improved prosthetic joint implants. This is because friction is believed to promote OA in two ways: high friction results in stronger shear stress on chondrocytes within the cartilage, leading to upregulation of cartilage-destroying enzymes, which in turn leads to higher friction at the degraded surface, and so on in a self-reinforcing cycle. Aside from this, the friction leads to the wearing of the cartilage and thus to the well-known symptoms of OA. Therefore, low friction (or reduction in cartilage friction via suitable external treatment) enables joint homeostasis by reducing shear stress on the chondrocytes (and the resulting catabolic response) while maintaining the normal stress essential for their proper anabolic function.

We recognised that any insight into the molecular picture must, first and foremost, be able to account for the low friction (coefficient of friction [μ] down to ~0.001) at the high pressures (which can reach 100 atm or higher) of the joints. However, direct measurements have indicated that the main molecular 'suspects' thought to constitute the lubricating boundary layer on cartilage, namely hyaluronic acid, lubricin, or phospholipids, (acting by themselves) do not provide especially good lubrication. Recently, we have discovered that hyaluronan (HA) which is attached to a surface (resembling its configuration at the outer cartilage surface) may form a complex with phosphatidylcholines (PCs), lipids that are ubiquitous in synovial joints to form robust boundary layers.[1] These layers act synergistically to provide the very low friction (μ≈0.001) characteristic of cartilage, at the highest physiological pressures, and contrast with surface-attached HA on its own which leads to considerably higher friction. The very low friction is ultimately due to the phosphocholine groups exposed by the HA/PC surface complexes; these groups are known to be strongly and highly hydrated and they lubricate via the recently elucidated hydration-lubrication mechanism.[2] In this mechanism, the hydration shells that surroundcharges (such as ions, or in the case of phosphocholine groups: zwitterions) have been demonstrated to provide extremely good lubrication up to physiologically high pressures.[2]

Our results thus point to a scenario[1,3] where HA, PCs, and lubricin, each with a very different role, act together synergistically to reduce friction of cartilage in articulating joints. HA, anchored at the outer surface of articular cartilage by lubricin molecules (which are known to be present in the outer superficial zone), complexes with joint phosphatidylcholines to provide the extreme boundary lubrication of synovial joints via the hydration-lubrication mechanism.[2] Our findings point to new clinical treatment modalities using, for example, suitable PC liposomes injected inter-particularly to augment the body's natural lubrication mechanism, and thus suppress the high friction which may promote OA as described above.

## Acknowledgments

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# DNA METHYLATION AND OSTEOARTHRITIS

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DNA methylation is one of the three epigenetic mechanisms that together regulate gene expression in multicellular organisms. In mammals, DNA methylation predominately involves the addition of a methyl group to a cytosine at a CpG dinucleotide catalysed by the DNA methyltransferase enzymes. Each cell type or tissue has its own unique DNA methylome, which undergo temporal and spatial changes during development, cell differentiation, and in response to external factors such as diet, exercise, and smoking. The effect of DNA methylation on gene expression is context dependent, with methylation within the gene promoter regions being associated with gene repression through effects on transcription factor and chromatin remodelling complex binding. Conversely, methylation within the gene body and three prime untranslated regions shows a positive correlation with gene expression and has been implicated in splicing and transcription from alternative promoters.[1,2]

Many common human diseases are associated with abnormal DNA methylation patterns, including cancer, rheumatoid arthritis, and osteoarthritis (OA). OA methylation studies have predominately focussed on cartilage due to the tissue's crucial role in OA disease process and because it is composed of a single cell type, the chondrocyte, and thus has a single methylome. There have been two types of study: 1) targeted analysis of promoter or enhancer regions of genes with known roles in cartilage biology or pathology; and 2) agnostic genome-wide analyses.[3] Both study types have compared methylation between OA and control non-OA cartilage or between the damaged and macroscopically normal cartilage from an OA joint, and together these studies have suggested that aberrant DNA methylation may play a part in the development and progression of OA.

Targeted analysis of the promoter of the OA genetic susceptibility gene *GDF5* has demonstrated that expression of this gene is regulated by DNA methylation.[4,5] *GDF5* is significantly upregulated in chondrocytes after exposure to demethylating agents and the transcriptional activity of the promoter is repressed by methylation *in vitro*. Furthermore, the *GDF5* promoter is demethylated and gene expression upregulated in hip and knee cartilage from OA patients compared to non-OA hip cartilage from neck-of-femur patients. This is mediated through methylation effects on transcription factor binding to the *GDF5* promoter, including the SP1 and SP3 proteins. Several genes whose altered expression in OA cartilage is associated with aberrant methylation have been identified in similar targeted analyses, include *SOX9*, *ADAMTS4*, and *MMP13* (Table 1).[3] However, these studies are limited in that they analyse methylation of a small number of CpG sites in genes already implicated in OA. To overcome this, several groups have performed genome-wide DNA methylome analysis in order to identify new pathways that may be important in the OA pathology.

Nine of the twelve OA methylome studies performed so far have used the Infinium® HumanMethylation BeadChip (Illumina Inc., CA, USA) 27K or 450K arrays, and in addition to the cartilage, the methylomes of cultured chondrocytes, femoral head bone, and trabecular bone have also been studied. We analysed the cartilage DNA methylome of 21 non-OA neck-of-femur fracture patients and macroscopically normal cartilage distal to the OA lesion from 23 OA hip and 73 OA knee patients.[6] Comparison of methylation between OA hip and OA knee cartilage indicated that they are epigenetically distinct, with 5,547 CpG sites having methylation differences of 10–74% between the two joint sites. There were 5,322 disease-associated CpG sites that had at least 10% difference in methylation between the control hip and OA hip cartilage, with these sites being enriched in genes involved in skeletal development and the TGF-β pathway. Furthermore,

the OA hip samples formed two discrete clusters that differed in methylation at 15,239 CpGs, with one cluster having promoter hypomethylation and increased expression of immune/inflammation associated genes including *IL1A*, *IL1B*, *IL6*, and *TNF*.[6,7] This inflammatory subgroup also has increased expression of the matrix degrading enzymes *MMP13* and *ADAMTS5*, and this data suggests that inflammation plays a critical role in OA pathogenesis, at least in a subgroup of patients.

**Table 1: Summary of targeted DNA methylation studies in osteoarthritis cartilage.**

| Function | Gene | Study | PMID | Technique | Cartilage samples | DNA meth | mRNA | Mechanism |
|---|---|---|---|---|---|---|---|---|
| Transcription | *SOX9* | Kim 2013 | 23225119 | BSQ, MSP | NOF versus OA hip | Increase | Decrease | CBF/NF-Y, CREB |
| ECM | *COL9A1* | Imagawa 2014 | 25048791 | BPSQ | NOF versus OA hip | Increase | Decrease | SOX9 |
| ECM degradation | *ADAMTS4* | Cheung 2009 | 18941754 | MSP | NOF versus OA hip | Decrease | Increase | |
| | *MMP3* | Roach 2005 | 16200590 | MSP | NOF versus OA hip | Decrease | Increase | |
| | *MMP9* | Roach 2005 | 16200590 | MSP | NOF versus OA hip | Decrease | Increase | |
| | *MMP13* | Bui 2012 | 22505473 | BSQ | NOF versus OA hip | Decrease | Increase | CREB |
| | | Hashimoto 2013 | 23417678 | BPSQ | NOF versus OA hip | Decrease | Increase | HIF2a |
| Signalling | *GDF5* | Reynard 2014 | 24861163 | BPSQ | NOF versus OA | Decrease | Increase | SP1, SP3, DEAF1, SUB1 |
| | *IL1B* | Hashimoto 2013 | 23417678 | BPSQ | NOF versus OA hip | Decrease | Increase | |
| | *IL8* | Tahahashi 2015 | 26521741 | BPSQ | NOF versus OA hip | Decrease | Increase | NF-kB, AP-1, C/EBPB |
| | *LEP* | Iliopoulos 2007 | 17502362 | BSQ | Preserved versus lesioned | Decrease | Increase | |
| | *PHLPP1* | Bradley 2016 | 26746148 | RRBS | NOF versus OA knee | Decrease | Increase | |
| | *SOST* | Papathanasiou 2015 | 26071314 | qMSP | KF versus OA knee | Decrease | Increase | BMP2, SMAD1/5/8 |
| Oxidative stress | *DIO2* | Bomer 2015 | 24695009 | Epityper | Preserved versus lesioned | Increase | Increase | |
| | *NOS2* | de Andres 2013 | 23239081 | BSQ, BPSQ | NOF versus OA hip | Decrease | Increase | NFKB subunit p65 |
| | *SOD2* | Scott 2010 | 20511611 | BSQ | NOF versus OA hip | Increase | Decrease | |

BSQ: bisulphite sequencing; MSP: methylation sensitive polymerase chain reaction; ECM: extracellular matrix; OA: osteoarthritis; BPSQ: bisulphite pyrosequencing; RRBS: reduced representation bisulphite sequencing; NOF: neck-of-femur fracture; KF: knee fracture.

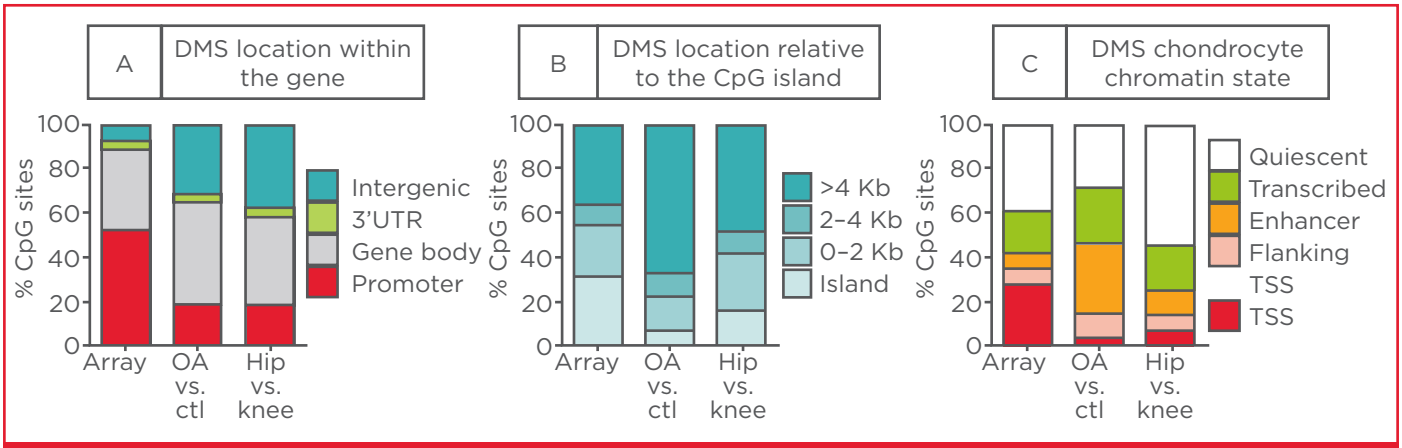


**Figure 1: Location of osteoarthritis-associated associated and joint-associated cartilage differentially methylated CpG sites (DMSs) identified by meta-analysis.**

A) Genic location of DMSs on the 450K methylation array (array, 422.070 CpGs), between OA hip and non-OA hip cartilage (OA vs. ctl, 3423 CpGs) and between OA hip and OA knee cartilage (hip vs. knee, 5781 CpGs)

B) Location of CpG sites on the array and those differentially methylated in cartilage relative to CpG islands

C) The chromatin state of cartilage DMSs in *in vitro* differentiated chondocytes

3'UTR: three prime untranslated regions; OA: osteoarthritis; TSS: transcriptional start site; ctl: control; DMS: differentially methylated CpG sites.

One surprising observation from the OA methylome studies is that the majority of the differentially methylated CpG sites (DMSs) are actually depleted in the gene promoters and CpG islands i.e. the regions examined in most of the targeted studies. Instead, the DMSs are enriched in thegene body, intergenic regions, and regions over 4 Kb away from CpG islands (Figure 1A, B).

Each methylome study has identified hundreds or thousands of DMSs, making it difficult to decide which of these sites to follow-up for additional functional studies. In order to identify DMSs for further analysis that are largely independent of environmental effects, we have performed a meta-analysis of three cartilage methylome studies from different geographical locations,[6,8,9] giving a total of 179 cartilage samples divided into five cartilage subtypes. We have created tracks of the DMSs from the meta-analysis that can be visualised using the UCSC genome browser; these tracks are available upon request. We are now looking at ways to integrate our methylation data from the meta-analysis with other freely available epigenetic datasets such as those generated by the Encyclopedia of DNA Elements (ENCODE) and National Institutes of Health (NIH) Roadmap Epigenomics projects in order to prioritise DMSs for further analysis. Analysis of chromatin state information from *in vitro* differentiated chondrocytes generated by the Roadmap Epigenomics project[10] confirmed that OA and joint associated DMSs are depleted in gene promoters but are significantly enriched in chondrogenic enhancer regions (Figure 1C). This suggests that instead of examining promoter methylation, future targeted OA methylation studies should be focussed on gene enhancers.

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# A EULAR DEFINITION OF ARTHRALGIA AT RISK FOR RHEUMATOID ARTHRITIS

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The field of rheumatoid arthritis (RA) is moving towards studies of the earliest phases of the disease. Before patients experience the first signs of clinical arthritis, they have a period of symptoms known as arthralgia. The issue is that these symptoms and signs, that are specific for RA in the phase of arthralgia (preceding clinical arthritis), have not been defined. A taskforce was initiated to harmonise this. By doing so, we allow the inclusion of a homogenous set of patients in future studies on this early disease phase, in which patients have symptoms but no clinical arthritis yet. Currently, different research groups use different definitions and consequently the results of different studies cannot be easily compared. This results in difficulty for observational studies but causes a large problem for the interpretation of findings of clinical trials.

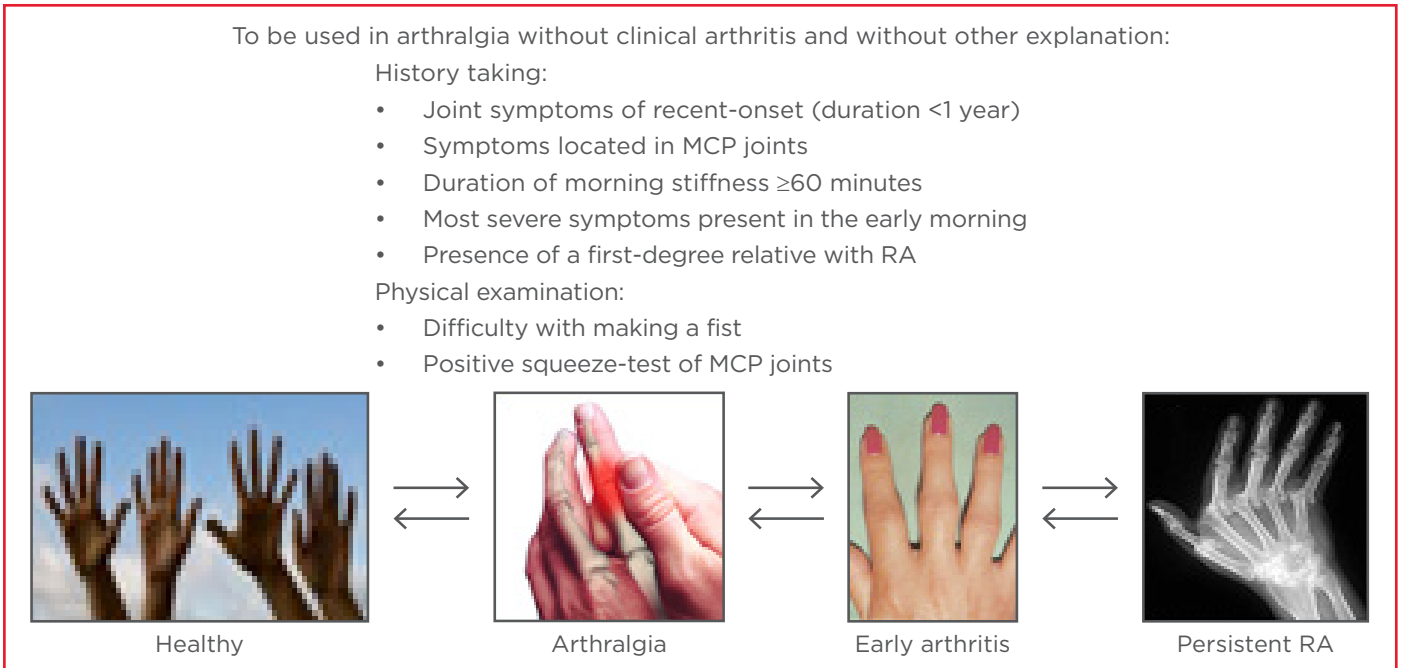


**Figure 1: Definition of arthralgia at risk of rheumatoid arthritis.**
MCP: metacarpophalangeal; RA: rheumatoid arthritis.

Thus the EULAR taskforce set out to derive a definition of arthralgia at risk for RA, with the ultimate aim of arriving at a definition that will define a homogeneous set of patients for scientific studies.

## METHODS

The clinical expertise of a group of European experts was used for reference. The project group consisted of 18 rheumatologists, 2 patients, 3 health professionals, and 1 fellow from 15 countries. The project was split into three phases and in each phase the clinical expertise was measured in different ways. The product of this is a definition of arthralgia at risk, which consists of seven clinical parameters.

## RESULTS

The definition included aspects of a clinical history and a physical examination (Figure 1); presence of three items correlates with a sensitivity of >90%, and presence of four items results in a specificity of >90%. The definition had very good accuracy (area under the curve of 0.92).

## FUTURE PERSPECTIVE

Further studies are now needed to determine the predictive accuracy of this definition, i.e. the predictive accuracy of the clinical criteria alone and when these are combined the results of additional investigations (serology, imaging). The importance of this work is that it is the first step towards criteria for imminent RA. This definition is the clinical patient description clinicians must be more aware of in clinical practice. The expectation is that if we add information from additional investigations to these clinical parameters (lab and/or imaging tests), we will be able to identify the patients with imminent RA with even higher accuracy.

The product of this taskforce is a consensus on the definition of arthralgia and the type of patients to be aware of following a clinical examination. This is an important step forward in the research field of 'pre-RA', a research field that, though in its infancy, is currently very active.

# FROM IMMUNOGENETICS TO A NEW TAXONOMY FOR CONNECTIVE TISSUE DISEASE

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Advances in our understanding of genetics and gene expression have allowed for the exponential advancement in our understanding of systemic lupus erythematosus (SLE) and the mechanisms behind the disease. Genome-wide association studies conducted in at least three ancestries have shown that in general the main risk loci for SLE are shared across frontiers.[1-3] Gene expression studies[4,5] have provided important information on the interferon signature and such genomic data can be used as a basis for the analysis of several systemic autoimmune diseases, expanding the data to other '-omics' sources. Most importantly, longitudinal analysis of gene expression data suggests a possibility to stratify patients with lupus into groups that may be studied for the best therapies to be adapted to their particular molecular pathways.[6] Bioinformatics have become increasingly important in the analysis and integration of the data. Furthermore, data can be used in connection with public data on the effects of genes or drugs in, for example, gene expression patterns to help identify new potential drugs, a strategy known as drug repurposing or repositioning. The PRECISESADS project[7] aims to reclassify the systemic autoimmune diseases through the

complete characterisation of several '-omics', including genomics, transcriptomics, epigenomics, metabolomics, and proteomics. The data will be analysed to identify clusters of individuals that share patterns across the data. The project includes 18 clinical centres from Europe, 5 pharmaceutical companies, and other academic partners. The latest results report the successful mirroring of 11 of the flow cytometers of various centres, a report that is now in press (Jamin et al., Autoimmun Rev).

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# ADJUVANTS, SILICONE, AND VACCINES; THE ROLE OF IMMUNE STIMULATION IN THE GENETICALLY PRONE PERSON FOR AUTOIMMUNITY

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Autoimmune diseases are multifactorial; genetic, hormonal (i.e. oestrogen, prolactin), immunological, and environmental factors all play in concert in an individual. This mosaic of autoimmunity explains:

1) The occurrence of different autoimmune diseases, even among the same family members[1]
2) Why a patient may develop a particular or multiple autoimmune diseases[2]
3) The timing of onset of autoimmune diseases

## GENETICS

Autoimmune diseases prevail in subjects with an aggressive immune system, i.e. *HLADRB1*[1,3] and among subjects carrying specific genes (e.g. *PTPN 22*).

## ADJUVANTS

Infections, as well as environmental factors, induce autoimmunity by acting as adjuvants (*adjuvare*: 'to help'). Freund's adjuvant consists of inactivated mycobacteria. Aluminium is the best adjuvant so far; it is incorporated into vaccines,[4-8] explaining how vaccines induce autoimmune diseases.[4] Aluminium also induced increased incidence of autoimmune diseases in reconstruction workers who worked on the clearance of the Twin Towers wreckage in the wake of the 9/11 attacks.[9] Another classic adjuvant, silicone, is represented in silicone breast implants, explaining the occurrence of autoimmune diseases following such procedures (rupture and bleeding).[10] The spectrum of autoimmune diseases induced by adjuvants is collectively termed ASIA syndrome.[5,7] Adjuvant chronic stimulation may also explain the increased incidence of lymphoma among patients with autoimmune diseases.[8] Animal models support the deleterious effects of adjuvants.[9,10]

## PERSONALISED MEDICINE

The knowledge of the genetic risk of developing autoimmune diseases and recognition of the adjuvant risk factors[11] alludes to a policy of personalised (precision) medicine for silicone implants and vaccines.[12-16]

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# BIOCHEMISTRY OF THE ENDOCANNABINOID SYSTEM AND ITS RELEVANCE FOR IMMUNE-MEDIATED DISEASES


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Nearly 30 years after the discovery of the psychoactive ingredient of *Cannabis sativa*, $\Delta^9$-tetrahydrocannabinol (THC) in 1964, the endogenous counterparts of THC were discovered and were collectively termed 'endocannabinoids' (eCBs). To date, N-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG) are widely recognised as the most bioactive eCBs, able to bind to and activate G protein-coupled Type 1 ($CB_1$) and Type 2 ($CB_2$) cannabinoid receptors, as well as other non-$CB_1$/non-$CB_2$ receptor targets. In addition to eCBs and their binding receptors, an array of proteins that synthesise, transport, and degrade these lipids have been identified in the last 20 years, altogether forming the so-called 'eCB system'. Unsurprisingly, eCBs have emerged as key regulators of human pathophysiology at multiple levels, both centrally and peripherally. In particular, they have been shown to regulate bone elongation and remodelling, as well as inflammation and adaptive/innate immunity. Notably, AEA and the eCB-like congener N-palmitoylethanolamine seem to be anti-inflammatory mediators, while 2-AG is implicated in both pro-inflammatory and anti-inflammatory functions. Moreover, the effects of eCBs on the immune system seem to be mostly

mediated by $CB_2$, more often expressed in immune cells, than by $CB_1$, and more often implicated in neurotransmission. Several studies have already investigated the role of the eCB system in different immune-mediated diseases, such as multiple sclerosis, Type 1 diabetes, and rheumatoid arthritis. In this summary, the data available in the literature were summarised and discussed. In addition, the role of eCB signalling in 10 female patients with systemic lupus erythematosus (SLE) and ten age and sex-matched healthy subjects has been presented. In these subjects, AEA, 2-AG, and N-palmitoylethanolamine plasma levels were quantified using liquid chromatography–tandem mass spectrometry, overall demonstrating an unprecedented alteration of eCB system in SLE patients. The audience to this presentation at EULAR appeared really interested in the topic, and appreciated the value of eCBs as novel molecular signatures of SLE with potential as disease biomarkers.

# INFLAMMATORY MEDIATORS IN INFLAMMATORY MYOPATHIES

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Idiopathic inflammatory myopathies (IIM) constitute a heterogeneous group of chronic disorders which include the four main subtypes recognised today: dermatomyositis (DM), polymyositis (PM), sporadic inclusion body myositis (IBM), and necrotising autoimmune myopathy (NAM). These diseases represent distinct pathological entities but share an autoimmune origin and often display chronic inflammation that damages the skeletal muscle tissue. In DM, membrane attack complexes form on blood vessel endothelia, causing capillary loss and muscle ischaemia. In PM/IBM, non-necrotic muscle fibres are invaded by autoaggressive CD8+ T cells. The perforins and granzymes they release result in cytotoxic necrosis of the fibres. In IBM, the inflammatory process is accompanied by degenerative phenomena and the accumulation of abnormal protein aggregates inside the muscle fibres. In NAM, the most prominent myopathological feature is muscle fibre necrosis, and generally less severe intramuscular inflammation can be observed.

The early immunopathogenic processes that cause the IIM remain poorly understood, however the detrimental role played by various mediators in sustaining inflammation becomes more and more clear. Induction of major histocompatibility complexes on the muscle fibre membranes makes IIM muscle fibres participate by becoming antigen presenters. B cells become activated and new types of autoantibodies are continuously being recognised in patient sera. Tissue sites and specific tissue constituents are marked for destruction, by upregulation of adhesion, co-stimulatory molecules, and complement deposition. Thus, both humoral and cell-mediated immune processes are involved in perpetuating the build-up of inflammation and the muscle tissue itself plays an active role by nurturing a pro-inflammatory tissue environment.

In the talk, the focus was placed upon cytokines as they are the master regulators of immune cell activation and migration. These small cell signalling proteins are known to be crucial factors in IIM, regulating inflammation from initiation toward progression. Cytokines can display both local muscle tissue activities as well as systemic effects through secretion into the blood stream. Ten essential cytokine sets were singled out based upon current knowledge of cytokine expression patterns in healthy individuals, versus IIM skeletal muscle tissues and patient serology. The list contained interferon (IFN)-α and β, tumour necrosis factor (TNF) family members

(TNF-α, BAFF), interleukins ([IL]-1, 2, 6, 12, 17, 23), and chemokines (CXCL9, 10, 11, CCL2). All of these factors are prominently expressed in patients, and many have been found to be associated with disease activity.

The potential of targeting these factors for selective immunosuppressive therapy was thoroughly discussed. For TNF-α, IFN-α, IL-1, and IL-6, clinical tests evaluating biologicals that block their activities have already become available and more are on the way. Results for infliximab and etanercept (both are therapeutic anti-TNF-α antibodies) and anakinra (a recombinant soluble IL-1 receptor agent) were varied, with responses ranging from clinical improvement to patients getting worse. A Phase I study evaluating sifalimumab (an anti-IFN-α therapeutic antibody) improved muscle strength in patients with DM/PM. Individual patients treated with the IL-6 receptor antibody tocilizumab reacted well to treatment. Interpretation of therapeutic responses reported in the available studies is however difficult due to small study size, different treatment regimen, and high drop-out due to disease deterioration.

It can be concluded that indeed the complex inflammatory network in IIM pinpoints targets for neutralisation. Selective immunosuppression is a valuable therapeutic approach and presents a necessary alternative for patients that do not respond to conventional treatments. Results so far are promising but have also shown the necessity for further subtyping of patients in order to develop future precision therapies and predict treatment outcome. It was suggested that for clinical evaluation, one should strive to isolate more homogeneous populations by prognostic subtyping of patients. This could be accomplished through in depth characterisation of myopathological patterns and profiling of autoantibodies and cytokines.

# SYSTEMATIC REVIEWS AND META-ANALYSES FOR DUMMIES: A TUTORIAL ON HOW, WHEN, AND WHY TO GET STARTED

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Prior to the 1990s, the task of combining data from multiple studies had been primarily based on narrative reviews; the problem with this was that a narrative review suffered from being subjective by nature, unlike a 'systematic review', which includes the application of scientific strategies that limit bias to the systematic assessment and critical appraisal of all relevant studies on a specific topic. The term 'meta-analysis' covers a series of statistical methods combining the results (with informative measures of heterogeneity) of several studies; not necessarily systematic, these can include 'simple' estimations across. However, a good meta-analysis can only be based on a thorough systematic review.[1]

Systematic reviews and meta-analyses are valuable and play an essential role when guideline panels need evidence synthesis in order to explicitly communicate benefits and harms, following a systematic review of all the available evidence. Also evidence-based research suggests no new studies should be planned without a prior systematic review of the existing evidence. Before initiating any searches or meta-analyses, it is important that there is a pre-specified protocol;[2] the goal is to design your evidence synthesis as a 'prospective project' (i.e. trying to counteract its retrospective nature). The protocol should be available via PROSPERO.[3] As part of good planning, key emphasis should be placed on defining the clinical question which can be clearly formulated using the PICOS framework; i.e. a clinically-relevant or policy-relevant question that takes into account

the patient/population, intervention, comparator, outcomes, and study design including both the benefit and harm of the intervention being studied.[1]

After the systematic review is complete, and a combined analysis has been provided, it is important to ensure that the reporting is correct[4] enabling the reader to judge the quality of the evidence.[1] The GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) working group have developed a system of rating quality of evidence that improves reliability in comparison to intuitive judgments about the evidence.[5] While looking at all the evidence after an appropriate 'meta-strategy', evidence-synthesis should explicitly delineate each of the following criteria that can lower the quality of the evidence (i.e. a consequence of reduced confidence in the estimate of effect): risk of bias/study limitations;risk of publication bias; imprecision; inconsistency of results; and indirectness.[5]

Finally, if you scrutinise the references given below you will be ready to begin.

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# ROLE OF ENDOTHELIAL TO MESENCHYMAL TRANSITION IN THE PATHOGENESIS OF THE VASCULAR ALTERATIONS IN SYSTEMIC SCLEROSIS


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## INTRODUCTION

The pathogenesis of the progressive fibrotic process and fibroproliferative vasculopathy in systemic sclerosis (SSc) is complex and despite extensive investigation, the exact mechanisms have remained elusive. Vascular involvement in SSc is being recognised as a crucial event in the disease process. Vascular abnormalities are universally present in SSc patients and often become apparent prior to the onset of tissue fibrosis. Although the fibroproliferative vasculopathy in SSc predominately involves the microvasculature, larger vessels are also involved. These observations collectively have led to the hypothesis that endothelial cell dysfunction may be the initial event in SSc pathogenesis.[1-3] The progressive vascular obliteration in SSc is caused by subendothelial accumulation of myofibroblasts and their production of abundant fibrotic tissue. Myofibroblasts, the cells ultimately responsible for tissue fibrosis and fibroproliferative vasculopathy in SSc, originate from several sources including expansion of quiescent tissue fibroblasts, transmigration and tissue accumulation of bone-marrow-derived circulating fibrocytes, and the phenotypic conversion of epithelial cells, adipocytes, or endothelial cells (EC) into activated myofibroblasts. The transdifferentiation of EC into myofibroblasts involves numerous and complex biochemical, molecular, and gene expression events collectively known as the endothelial to mesenchymal transition (EndoMT).

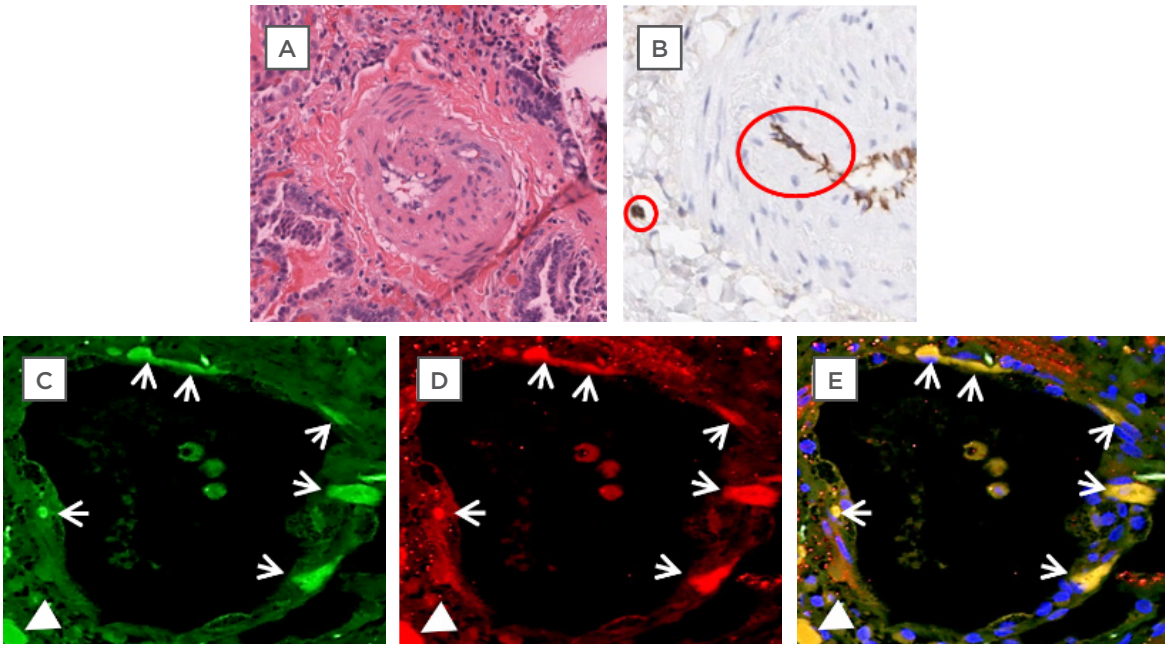


**Figure 1: Immunohistology and confocal microscopy staining of medium-sized pulmonary arteries in systemic sclerosis-associated pulmonary fibrosis lung tissues.**
A) Histopathology of a pulmonary arteriole showing severe proliferative vasculopathy with luminal occlusion.
B) CD31-expressing cells (brown staining) in the subendothelial region of a small pulmonary arteriole and in the lung parenchyma (red circles).
C–E) small arteriole in affected SSc lung.
C) staining for vWF (green).
D) staining for α-SMA (red).
E) overlay (yellow). Note numerous cells in the endothelial lining (arrows) and one cell in the subendothelial tissue (arrowhead) displaying co-expression of EC (vWF) and myofibroblast (α-SMA) molecular markers as evidenced by the yellow colour in the overlay image.
SSc: systemic sclerosis; vWF: von Willebrand factor; α-SMA: α-smooth muscle actin.
*Adapted from Mendoza F et al.*[8]

Despite the demonstration of the occurrence of EndoMT in experimentally-induced cardiac, renal, and pulmonary fibrosis, and in several human disorders as described in a recent review,[4] the contribution of EndoMT to the pathogenesis of tissue fibrosis and fibroproliferative vasculopathy in SSc has not been studied extensively. However, recent experimental evidence has appeared providing strong support to the concept that EndoMT plays a role in the development of SSc-associated interstitial lung disease (SSc-ILD) and SSc-associated pulmonary arterial hypertension (SSc-PAH).

## Demonstration of Endothelial to Mesenchymal Transition in Primary and in Systemic Sclerosis Associated Pulmonary Arterial Hypertension

Two recent studies have examined the role of EndoMT in the pathogenesis of pulmonary arterial hypertension (PAH). The first study applied transmission electron microscopy and correlative light and scanning electron microscopy, providing unequivocal ultrastructural level evidence of ongoing dynamic EndoMT in lung tissue samples from patients with primary PAH.[5] This study demonstrated that typical EC, identified by the presence of Weibel–Palade bodies, acquired

expression of the myofibroblast-specific marker, α-smooth muscle actin (α-SMA), and displayed invaginations into the neointima of the abnormal pulmonary arterioles. In the second study, Good et al.[6] assessed EndoMT in the pulmonary arterioles in lung tissues from patients with SSc-PAH. Examination of the cellular phenotype in intimal and plexiform lesions from PAH lungs showed the co-expression of endothelial (CD31, CD34, vascular endothelial-cadherin) and mesenchymal (α-SMA) markers in numerous cells. A quantitative assessment of the co-expression of von Willebrand factor (vWF) and α-SMA indicated that up to 4% of pulmonary arterioles in the lungs of patients with SSc-PAH displayed co-expression of EC and mesenchymal cell markers. Furthermore, the protein and messenger RNA expression patterns confirmed a key role of EndoMT in SSc-PAH pathogenesis. The novel observations described in these two studies provide conclusive evidence for the occurrence of EndoMT in small and medium size arterioles of lung tissues from patients with both primary PAH and SSc-PAH as discussed recently.[7]

### Demonstration of Endothelial to Mesenchymal Transition in Primary and in Systemic Sclerosis Associated Interstitial Lung Disease

We recently performed a study to examine the role of EndoMT in the fibrotic process of SSc-ILD.[8] In this study lung tissues from six patients with SSc and pulmonary fibrosis and two normal lung controls were examined by histopathology, immunohistochemistry, and confocal laser microscopy for the simultaneous expression of markers of EC (CD31 and vWF) and myofibroblasts (α-SMA or Type I collagen). Immunohistology studies showed expression of the EC marker CD31/PECAM in mesenchymal cells embedded within the neointima of small pulmonary arteries as well as in the parenchymal fibrotic areas in the six SSc lung specimens. These observations demonstrated for the first time the presence of cells carrying EC molecular markers embedded within the fibrotic lung parenchyma in all SSc-ILD samples examined. This study also demonstrated the co-expression of CD31 or vWF with the mesenchymal markers, collagen Type I, or α-SMA in numerous EC lining the small and medium sized pulmonary arteries employing confocal laser microscopy as illustrated in Figure 1. These findings were not present in the small or medium sized arteries of normal lungs. The results demonstrated that EC co-expressing EC-specific and myofibroblastic cell markers are present in the endothelium of small pulmonary arteries from patients with SSc-ILD. These results also suggest that mesenchymal cells of endothelial origin are likely to be responsible for the production and accumulation of subendothelial fibrotic tissue in the affected vessels that in turn result in their luminal obliteration. These observations were confirmed by an extensive assessment of the differences in gene expression patterns between microvascular EC isolated from normal lungs compared to microvascular EC isolated from lungs from patients with SSc-ILD. The gene expression profile of immunopurified CD31+/CD102+ EC from SSc-ILD lung tissues demonstrated up to 21-times increased expression of COL1A1 and up to 26-times increased expression of COL3A1 in the EC purified from lungs of SSc patients. The expression of profibrotic genes such as *FN1*, *ACTA2* (α-SMA), *TGFB1*, and *CTGF*, and that of several EndoMT-related genes such as *SNAI2* and *TWIST* was also substantially increased in the EC isolated from the lungs of SSc patients. The results of the extensive study performed in lung tissues from patients with SSc-ILD provide conclusive evidence for the occurrence of EndoMT during the fibrotic process affecting the lungs in SSc. Furthermore, the recent demonstration that transforming growth factor beta and endothelin 1, crucial molecules involved in SSc pathogenesis, are capable of inducing EndoMT,[9] provides additional support to the notion that EndoMT may play an important role in the pathogenesis of SSc-associated tissue fibrosis and fibroproliferative vasculopathy as discussed recently.[7]

## CONCLUDING REMARKS

The results of the studies reviewed here indicate that EndoMT plays a role in the pathogenesis of SSc-ILD and SSc-PAH. It suggests that a greater understanding of the EndoMT molecular mechanisms and its pharmacological

modulation may represent a novel therapeutic approach for the devastating effects, the high mortality of SSc-associated tissue fibrosis, and fibroproliferative vasculopathy.

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# FREE RADICAL SIGNALLING BEHIND THE MUSCLE WEAKNESS ASSOCIATED WITH RHEUMATOID ARTHRITIS


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In addition to the primary symptoms arising from inflammatory processes in the joints, muscle weakness and impaired work capacity are commonly reported by patients with rheumatoid arthritis (RA). Reduced muscle strength has always been more or less synonymous with decreased muscle mass. However, our data show that muscle weakness associated with RA is not only a result of atrophic muscles. Instead, intracellular (intrinsic) muscle dysfunction appears to be an important factor behind arthritis-induced muscle weakness. In fact, in 1996 Helliwell and Jackson[1] showed that the reduced grip strength of patients with RA was larger than could be explained by the reduction in muscle size. Accordingly, Helliwell and Jackson stated that "doubts remain about the quality of muscle in RA."

Here we examined the intrinsic skeletal muscle contractile function in mice (collagen-induced arthritis [CIA]) and rats (adjuvant-induced arthritis [AIA]) with arthritis (see Figure 1 for proposed model). Skeletal muscle contraction is dependent on $Ca^{2+}$ release from the sarcoplasmic reticulum (SR) leading to increased $Ca^{2+}$ concentration in the cytosol. In simple terms, the higher the $Ca^{2+}$ concentration, the greater the force that can be generated. This is valid until maximal force is reached and all 'motors' (cross-bridges) are activated. The ryanodine receptor 1 (RyR1), localised in the SR membrane, is the major $Ca^{2+}$ release channel in skeletal muscle. Intriguingly, we observed a substantial increase in $Ca^{2+}$ release accompanied by ~30% reduction in specific force (i.e. force per cross-sectional area) in both fast-twitch and slow-twitch skeletal muscle from rodents with arthritis.[2-4]

The RyR1 is sensitive to redox modifications, both oxidation and nitrosylation have been shown to increase the open probability of the channel.[5-7] We observed a 3-fold increase in the 3-nitrotyrosine (3-NT) levels, a marker of peroxynitrite ($ONOO^{\bullet-}$), on the RyR1 complex. $ONOO^{\bullet-}$ is formed by the reaction between nitric oxide (NO) and superoxide ($O_2^{\bullet-}$). Higher levels of

NO synthase type 1 (NOS1/nNOS) was detected in mice and rats with RA. We also found increased NOS1 levels in patients with RA.[3] Furthermore, we detected 5-fold more NOS1 bound to RyR1 in CIA muscle than in controls. Intriguingly, NOS1 can produce both NO and $O_2^{\bullet-}$ and this may directly increase ONOO- formation.[8] In addition, we detected increased levels of NOX2/gp91phox, which produces $O_2^{\bullet-}$, and TNF-α, thereby increasing the production of oxidants, in muscle from rodents with arthritis.[2] Thus, ONOO-induced RyR1 modifications could explain the facilitated SR $Ca^{2+}$ release observed in muscle from mice with arthritis, but what about the decreased force?

We observed no marked atrophy or loss in actin or myosin content in muscles from rodents with arthritis.[2-4] Nevertheless, actin showed a 4-fold increase in the $ONOO^{\bullet-}$ marker 3-NT. No other makers of oxidative stress, e.g. malondialdehyde or carbonylation were observed. The contractile machinery (actin-myosin interactions) was studied in detail by bypassing the normal activation (i.e. excitation-contraction coupling with RyR1 opening and $Ca^{2+}$ release) and directly activating myofibrils and measuring force production with atomic force cantilevers. The active force in myofibrils from arthritis mice was markedly lower (~50%) than in myofibrils of healthy controls.[3] Thus, the muscle weakness in muscles from rodents with RA is caused by impairments in the contractile machinery.

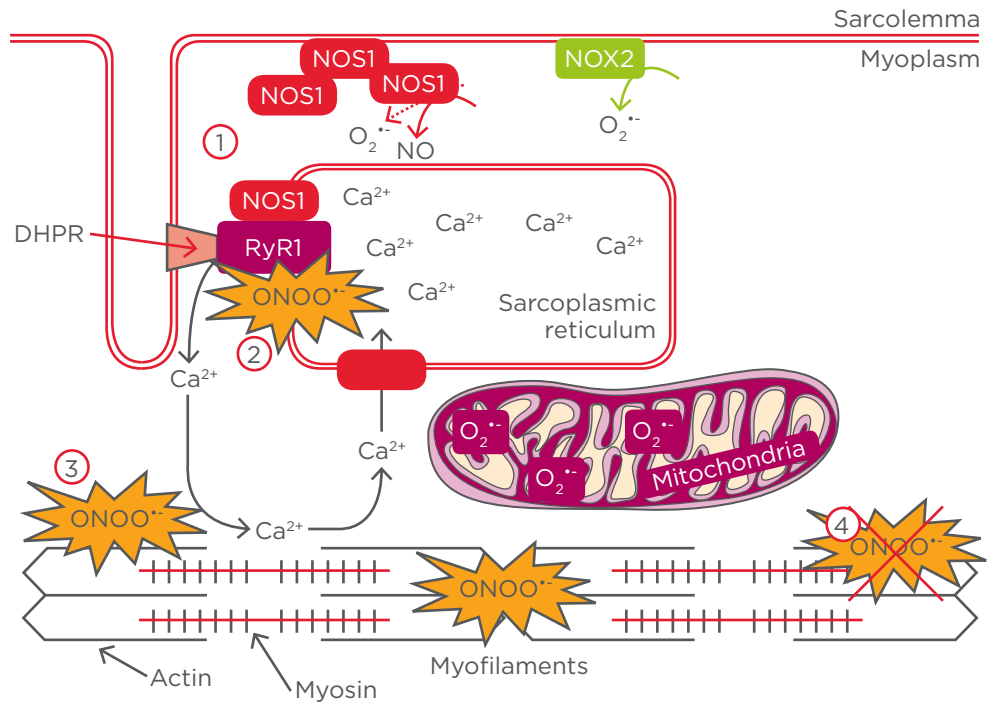


**Figure 1: A proposed model of intramuscular mechanisms behind muscle weakness in arthritis and a tentative treatment.**

1. NOS1 is globally increased in arthritic muscle and more NOS1 is associated with the RyR1 protein complex.

2. This together with other sources of $O2^{\bullet-}$ leads to $ONOO^{\bullet-}$ modifications of the RyR1 protein complex and increased SR $Ca^{2+}$ release during contractions, which further activates the $Ca^{2+}$-sensitive NOS1.

3. The increased amounts of $ONOO^{\bullet-}$ attack myofibrillar proteins, such as actin, and cause contractile impairment and muscle weakness.

4. Treatment with antioxidants prevents the $ONOO^{\bullet-}$ modifications of actin and preserves muscle force.

NOS: nitric oxide synthase; RyR: ryanodine receptor; $ONOO^{\bullet-}$: peroxynitrite; DHPR: dihydropyridine receptor; $O_2^{\bullet-}$: superoxide.

We have begun to examine whether arthritis-induced muscle weakness can be counteracted with pharmacological and/or non-pharmacological interventions. So far, a 3-week treatment with the antioxidant EUK-134 (superoxide dismutase/catalase mimetic) in rats with AIA was shown to lower the amount of 3-NT on actin and to prevent the loss of muscle force production.[2] Next, we want to study the intrinsic skeletal muscle function in patients with RA. Other groups of patients with chronic inflammatory disease, such as myositis are also of great interest. Thus, our overall pursuit to improve contractile function and work capacity in subjects afflicted by inflammatory disease-induced muscle weakness continues.

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# HOW TO TREAT SJÖGREN'S SYNDROME

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Primary Sjögren's syndrome (PSS) is a complex immunological condition characterised by prevalent involvement of the exocrine glands (sicca syndrome) accompanied by systemic features due to prevalent activation of the humoral immune response. PSS treatment requires a multidisciplinary approach that involves rheumatologists, ophthalmologists, oral specialists, and in some cases psychological support. Baseline assessment by the ophthalmologist and oral medicine specialist should be endorsed at the time of diagnosis and afterward, if the management of the ocular complications requires expert advice, for example in cases of severe dry eyes, blepharitis non-responsive to first-line treatments, or inflammatory complications of the conjunctiva or mouth. Generic recommendations applicable to all patients with PSS include the maintenance of excellent oral hygiene, regular dentist examinations, and use of high fluoride toothpastes. Patients should be advised to stop or significantly reduce the consumption of fizzy or sugared drinks, to avoid eating between meals, humidify the environment, and increase the water intake. Counselling on the substitution/suspension of dryness-inducing medications and introduction of moderate aerobic exercise should also be provided.

Sicca syndrome can manifest in all the systems lubricated by exocrine glands, such as eyes, mouth, skin, gastrointestinal, vaginal, and respiratory tract. Therapeutic approaches rely on the principles of conserving the glandular function, replacing it when lost, and stimulating it where possible. Treating inflammation or infectious complications is also recommended. All patients, in particular those who present residual glandular function, should be offered a course of pilocarpine, a parasympathetic agent, agonist of the muscarinic receptors. Unfortunately, this drug is poorly tolerated and patients are often unable to maintain its use at therapeutic doses for an extended period of time. Mechanical and electrical glandular stimulation has been used for the mouth with

variable results. The use of eye drops and saliva substitutes should be advised. The use of compounds able to provide lubrication of the vaginal channel can be advised, together with hormonal creams.

In cases of severe xerophthalmia or in the presence of persistent inflammation, the therapeutic plan, which often involves use of cyclosporine or steroid eye drops, punctual plug insertion, or use of special contact lenses, should be devised in agreement and under the guidance of a specialist ophthalmologist. Infectious complications of the mouth can be mainly addressed with the use of anti-fungal topical compounds.

There are no approved drugs for PSS management and severe systemic manifestations are treated with variable results with disease-modifying anti-rheumatic drugs (DMARDs). Reports on the successful use of methotrexate, mycophenolate mofetil, azathioprine, and in the most severe cases cyclophosphamide, have been made. Hydroxychloroquine use is supported despite the lack of evidence on efficacy in randomised clinical trials. Use of steroids to address fatigue is not favoured and in general, steroid use should be limited in PSS patients to short courses. In this form steroids can be used to address recurrent parotid swelling (also by local instillation in the glandular duct) or disease flares characterised by arthritis, cutaneous, or haematological manifestations. Staging and management of lymphoma should be agreed with a specialist haematologist and might include the use of B cell target therapies in association with chemotherapy.

A series of biological compounds have been made available in the context of clinical trials and encouraging, but not definitive, results have been observed with abatacept and rituximab in open-label studies. Discussions are taking place to refine the measure of outcome in clinical trials and identify biological stratifiers for drug response. The large academic effort toward a better understanding of this complex disease, together with the novel interest of the pharmaceutical industry to address the therapeutic void in PSS has finally opened a new exciting scenario for this disease.

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EDITOR'S PICK

Diagnosis of Sjögren's syndrome has been made difficult as it exhibits a similar symptomatology to other autoimmune conditions. This is just one aspect of the disorder that has frustrated attempts to better understand its genetic, environmental, and immunological basis. In the following paper, Wanchoo et al. provide some welcome headway by pointing to the failure of TAM receptor tyrosine kinase signalling as a potential cause underlying the development of Sjögren's syndrome. This is an informative and important read that will no doubt provide researchers with an invaluable insight into the disease pathogenesis, and offer a step towards creating a better understanding of the syndrome.

# TYRO3, AXL, AND MERTK RECEPTOR TYROSINE KINASES: IS THERE EVIDENCE OF DIRECT INVOLVEMENT IN DEVELOPMENT AND ONSET OF SJÖGREN'S SYNDROME?

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## ABSTRACT

Sjögren's syndrome (SjS) is a chronic, progressive, systemic, human autoimmune disease in which an auto-inflammatory process within the salivary and lacrimal glands results in loss of saliva and tear production, respectively. In-depth analyses of the autoimmune process in humans and animal models of SjS substantiates one of the more important pathoaetiological pathways: an increased level of glandular apoptosis and/or cell lysis. We have hypothesised that failure in clearance of dying cells by macrophages, dendritic cells, and neighbouring tissues results in a sustained innate inflammatory response that transitions to autoimmunity. Since the intrinsic inhibition of inflammation following phagocytosis of dying cells is a function of a family of three receptor tyrosine kinases (RTKs) known as the TAM (Tyro3, Axl, and Mertk), we put forward the following hypothesis: based on published information and analysis of our public microarray data, the failure of TAM RTK signalling, specifically in activating suppressor of cytokine signalling (SOCS) 1 and SOCS3 (which are inhibitors of immune responses), may lead to autoimmunity, and specifically, to SjS-like disease.

Keywords: Sjögren's syndrome (SjS), autoimmunity, TAM (Tyro3, Axl, and Mertk), receptor tyrosine kinase (RTK), apoptosis, phagocytosis.

## INTRODUCTION

Sjögren's syndrome (SjS) is a chronic, systemic, human autoimmune disease in which an immunological attack against the salivary and lacrimal glands results in dry mouth (stomatitis sicca/xerostomia) and dry eye (keratoconjunctivitis sicca/xerophthalmia) disease(s), respectively.[1] Despite efforts to define the genetic, environmental, and immunological basis of SjS, the underlying aetiology remains poorly defined, in part due to diagnoses being made after the onset of the overt disease, which is then further deconvoluted based on disease phenotypes and symptoms. Additionally, disease symptoms can be classified into primary SjS, disease progression symptomatic of xerostomia and/or xerophthalmia, or secondary SjS, SjS disease symptoms compounded from other forms of autoimmunity including lupus, multiple sclerosis, rheumatic arthritis, or other rheumatic autoimmune diseases. In an attempt to better define the nature of autoimmunity in SjS, a variety of mouse models exhibiting various aspects of SjS have been identified and studied extensively, particularly as a means to investigate events associated with early-stage disease.[2] One of the more intensively studied models of SjS is the non-obese diabetic (NOD) mouse,[3] and this model has been shown to closely mimic the generalised SjS phenotype despite the fact that SjS shows great disparities among human patients.

In-depth insight into the autoimmune process in human SjS and animal models with SjS-like diseases substantiates one of the main aetiological pathophysiological pathways: an increased, non-compensated, glandular apoptosis and lysis of acinar tissue. Under normal circumstances, the clearance of apoptotic cells by macrophages, dendritic cells (DC), and neighbouring tissue initiates a protective immunosuppressive and anti-inflammatory activity to regulate inflammation, whereas the clearance of lytic cells and the defective clearance of apoptotic cells can activate inflammatory responses that may result in autoimmunity.[4] The intrinsic inhibition of inflammation following phagocytosis of apoptotic cells is mediated by a family of receptor tyrosine kinases (RTKs) and represents a critical mechanism for regulating inflammation and self-recognition, primarily during innate immune responses.[5,6] The focus of this review is to provide an in-depth analysis of RTKs and their functions in apoptosis and autoimmunity, specifically the autoimmune process of SjS.

## SJÖGREN'S SYNDROME IN NON-OBESE DIABETIC-DERIVED ANIMAL MODELS

Seminal studies and reviews have extensively discussed various animal models of SjS.[3,7,8] Using the NOD and NOD-derived mice, our studies were able to define the genetic predisposition for development and onset of SjS-like disease in both, and offer interesting contrasts and similarities with human SjS. At first glance, SjS-like disease in mice appears to have only a weak association with major histocompatibility complex (MHC) Class I and Class II genes,[9,10] thus apparently mimicking SjS in humans. However, recent human SjS genome-wide association study data have indicated that the highest statistically valued single nucleotide polymorphism association lies within the human leukocyte antigen (HLA) region.[11] Based on extensive studies using our two related SjS-susceptible ($SjS^s$) models, NOD/LtJ and C57BL/6.NOD-*Aec1Aec2*, we have identified multiple physiological, molecular, and immunological features defining the underlying pathophysiology,[3] thus permitting us to divide the disease process into a series of distinct, consecutive, temporal, yet overlapping phases. In the earliest phase (0–8 weeks), multiple aberrant physiological and biochemical activities predominate, associated with changes in cellular junctions, focal adhesions, and increased acinar cell apoptosis and lysis. In the subsequent phase (8–12 weeks), a strong innate autonomous cell response occurs involving the activation of interferon (IFN)-responsive genes in conjunction with the appearance first of macrophages and DC, then of transitional lymphocytes that initiate formation of the signature histological lymphocytic foci consisting mostly of $CD4^+$ T and $B220^+$ B cells. In the late phase (12–20 weeks and onward), characterised by an adaptive immune response, an overt clinical disease is seen, defined by a progressive, measurable loss of salivary and lacrimal gland secretory function. This exocrine gland dysfunction in SjS is thought to result from a combination of pro-inflammatory cytokine activity, synthesis of auto-antibodies reactive with the muscarinic acetylcholine and beta adrenergic receptors, plus the direct action of infiltrating T cells, including both $CD4^+$ T helper 1 and 17 cells.[12] Nevertheless, specific gene knockout and recombinant inbred lines have indicated that the

disease progression can be arrested at various stages of development and onset.

## TYRO3, AXL, AND MERTK RECEPTOR TYROSINE KINASES: STRUCTURE, LIGANDS, AND SIGNALLING

Tyro3, Axl, and Mertk (TAM) RTKs consist of a cytosolic tyrosine kinase domain, a single hydrophobic transmembrane domain, two extracellular immunoglobulin (Ig)-like domains, and two extracellular fibronectin Type III domains.[13] The Ig-like domains interact with the TAM ligands, either growth arrest-specific protein 6 (Gas6) or protein S (Pros1),[14] through two C-terminal extracellular laminin G domains in a heterotetrameric complex.[15] The TAM ligands bind to the plasma membrane of apoptotic cells at an exposed phosphatidylserine (PtdSer) site through the N-terminus gamma-carboxyglutamic acid domain. Vitamin K reduces the 4-carbon of glutamate in the gamma-carboxyglutamic acid domain, increasing its ability to bind the negatively charged PtdSer.[16] Binding of the TAM RTKs to Gas6 or Pros1 induces autophosphorylation of cytosolic tyrosine residues, which in turn increases phosphorylation of substrates and recruitment of signalling molecules.

TAM RTKs play multiple critical roles in regulating innate immune responses, specifically inhibiting inflammatory responses that might otherwise develop from the phagocytosis of apoptotic cells.[4] Phosphoinositide 3-kinase binds with all TAM RTKs and is responsible for the recruitment of several downstream proteins including the mammalian target of rapamycin.[17] Phospholipase C and growth factor receptor-bound protein 2 bind with Mertk and Axl, a process that regulates calcium channels,[18] while ran-binding protein M associates with Axl and Tyro3, but this binding has an unknown function.[19,20] Although some molecular pathways can be regulated by more than one of the TAM RTKs, others have been shown to associate with a specific RTK. For example, Shc,[21] Vav1,[22] and activated cell division control protein 42 kinase 1[22] associate with Mertk, while Nck2,[19] SOCS 1,[19,23,24] S-locus receptor kinase (Src)/lymphoid cell kinase,[18] and C1-Ten[25] associate with Axl, and protein phosphatase 1[20,26] and Src family kinases[27] with Tyro3. Dysfunction of TAM RTK signalling can result in aberrant phagocytosis of apoptotic particles and membranes, primarily by antigen-presenting cells, leading to positive selection and over-expansion of myeloid and lymphoid cell populations' targeting self-antigens that can transition subsequently to autoimmunity.[28]

## TYRO3, AXL, AND MERTK SIGNALLING IN CLEARANCE OF APOPTOTIC CELLS

The TAM RTK receptors, together with their major ligands and activations of the SOCS1 and SOCS3 molecules, play critical roles in regulating innate immune responses, particularly inhibiting inflammatory responses associated with phagocytosis of apoptotic cells.[4,29] A function of GAS6 and Pros1 is to link TAM receptors to PtdSer residues expressed on the membranes of apoptotic cells and debris, facilitating phagocytosis and non-stimulatory degradation.[17] The loss of TAM RTK receptor activations can result in aberrant phagocytosis of apoptotic cells and membranes, primarily in antigen-presenting cells, leading to subsequent over-expansion of myeloid and lymphoid cell populations, which can transition to subsequent autoimmunity[6] or its exacerbation.[28,30] Loss of normal TAM RTK receptor signalling is also characterised by upregulations of several downstream signalling pathways and pro-inflammatory factors, including toll-like receptors, p38-Mapk, Erk1/2, Traf3, Traf6, and AP-1 transcription factors that regulate multiple pro-inflammatory bioprocesses, including expression of IFN-responsive genes. Our previous studies have shown, by microarray analyses, that the genes of these factors are upregulated in the salivary glands of B6.NOD-*Aec1Aec2* mice.[31-33] Thus, the TAM RTKs appear to connect several early phase pathophysiological processes observed in SjS[s] mice prior to onset of the autoimmune phase of disease.

Apoptosis is one of the major biological events that occur in the exocrine glands of human and animal models of SjS. Two factors shown to be associated with acinar tissue apoptosis are α-fodrin proteolysis and Fas/Fas-ligand interaction. First, salivary glands of NFS/sld mice appear to express the 120 kDa fragment of α-fodrin as an organ-specific autoantigen.[34,35] In addition, specific autoantibodies against α-fodrin have been detected in NOD mice, and these antibodies correlated with the levels of sialadenitis.[36] Secondly, studies have indicated that the interaction of Fas and Fas-ligand can facilitate a cascade of events that lead to the activation of caspases and proteinases, which serve to fragment DNA.[37] Various studies have

indicated that the Fas antigen is expressed in ductal epithelial cells of SjS patients with severe sialadenitis, but not in patients with mild sialadenitis, suggesting that Fas-positive ductal cells provide a good target for effector T cells.[38,39] Okuma at al.[40] intricately demonstrated that dysfunction of epithelial cells, but not haematopoietic cells exhibiting a disruption of Stat3-mediated IκB-ζ induction, resulted in the downstream activation of self-reactive lymphocytes involved in SjS development.[40] Anintriguing question plaguing the understanding of autoimmune diseases such as SjS relates to how intracellular self-proteins become autoantigens, presented as dominant neoantigens, and recognised by immune cells following apoptosis. Rosen et al.[41] suggested that cellular apoptosis is one of the early events in SjS development, based on redistribution of molecules within the subcellular compartments. Small membrane blebs were shown to contain the Ro-52 kDa molecule, along with other molecules such as calreticulin, which are normally present within the endoplasmic reticulum lumen. Acinar cellular apoptosis is an ongoing process in SjS that is associated with glandular infiltration by leukocytes, as prevention of high apoptosis in the exocrine glands also prevents leukocyte infiltrations and development of pathology. Thus, it seems imperative to focus on the precise relationship between apoptosis and the normal mechanisms for proper clearance of apoptotic debris, as we and others have shown what are perceived to be deficient regulatory mechanisms associated with the clearance of apoptotic debris;[42-46] therefore, the focus on TAM RTK receptor-mediated biological mechanisms is discussed below.

## TYRO3, AXL, AND MERTK SIGNALLING IN AUTOIMMUNITY

Expression and immune recognition of self versus non-self antigens is a process that requires constant surveillance to prevent auto-inflammation and/or autoimmunity in both predisposed and non-predisposed individuals. The TAM RTKs, via the production primarily of SOCS1 and SOCS3 molecules, represent a powerful system for regulating possible innate and adaptive responses; thus, any failure in the normal function of the TAM RTK–SOCS axis establishes an environment conducive to autoimmune activity, some of which can progress to clinical disease. A close examination of our transcriptomic data publically available at the Gene Expression Omnibus (GSE15640, GSE36378) indicated that the TAM RTK receptors and their ligands are downregulated throughout the entire process of disease progression, as depicted in Figure 1, thereby negating any normal positive feedback during apoptotic cell clearance. Data published by Lu and Lemke[28] indicated that mice deficient in TAM RTK expressions appear to show normal peripheral lymphoid organs at birth, but by 4 weeks of age they display a marked increase in spleen and lymph node size relative to wild-type, and by 1 year of age, the spleen weights were on average 10-times that of the wild-type. The aberrant growth of peripheral lymphoid organs was primarily due to hyperproliferation and constitutively activated B and T cells.[28] Nevertheless, Caraux et al.[47] demonstrated that all three TAM RTK receptors plus their ligands (Gas6 and Pros1) are expressed by natural killer (NK) cells and bone marrow stromal cells, respectively, pointing to the fact that these receptors appear essential in the formation of the NK cell receptor repertoire and in the functional maturation of NK cells in the spleen, whereas Gas6 and Pros1 promoted the growth and maturation of NK cell precursors *in vitro*. These data suggest a crucial role of TAM receptors and their ligands in proliferation and maturation of lymphoid cells, especially in inhibiting production of autoreactive lymphocytes. As predicated, therefore, such mutants exhibit a broad spectrum of autoimmunity, including symptom-like clinical pathologies associated withrheumatic arthritis, pemphigus vulgaris, and systemic lupus erythematosus with elevated blood titres of antibodies directed against normal cellular antigens, including nucleoproteins and double-stranded DNA.[28] It must also be noted that the *Socs3* gene knockout mouse is a lethal mutation, suggesting that these systems have additional roles in overall health and development.

## TYRO3, AXL, AND MERTK SIGNALLING IN SJÖGREN'S SYNDROME

In recent studies, Wallet et al.[48,49] reported that DC from NOD mice deficient in Mertk expression not only played a pivotal role in negative selection of T cells within the thymus, but also failed to exhibit apoptotic cell-induced immunosuppression, resulting in a more severe

Type 1 diabetes. The significance of these studies by Wallet and colleagues is critical due to the fact that we have previously reported a decreased production of SOCS3, together with a complete lack of any detectable upregulated *Socs1*/SOCS1 expression in the salivary glands of C57BL/6.NOD-*Aec1Aec2* mice.[50] This is highlighted even more by the fact that in the salivary glands of SjS-non-susceptible (SjS$^{NS}$) B6 mice, *Socs3* is one of the highest upregulated genes observed within our microarray analysis (Figure 2). It is well documented that salivary glands of B6 mice, like most strains of inbred mice, will show varying degrees of histological evidence for lymphocytic infiltration as the mice age, but the levels of such infiltration are usually low and the composition of the infiltrate is quite different from that seen in C57BL/6.NOD-*Aec1Aec2* and NOD/LtJ mice. Because the expression of *Socs1* and *Socs3* are strongly associated with activation of the TAM RTK receptors, these data are consistent with the concept that the TAM RTK signalling pathways in macrophages and DC of the parental B6 mice are capable of inhibiting subsequent inflammatory responses despite infiltration of salivary glands by CD4$^+$ T cells, whereas this is not achieved in our SjS$^S$ mice. Most importantly, TAM RTKs and their signalling pathways lead directly to transcription of *Socs1* and *Socs3* genes, and SOCS3 is known to play a critical role in inhibiting pro-inflammatory responses induced by macrophages and DC following engulfment of apoptotic (or infected) cells, thereby acting as a 'go/no go' system for innate to adaptive immune responses. The focus of the following discussion is to provide logical support to the hypothesis that the TAM receptors and their regulatory ligands represent a critical bioprocess for controlling immune homeostasis during the innate phase of an immune response. However, in the development of SjS-like disease, the normal bioprocess is either dysregulated, subverted, or actively suppressed.

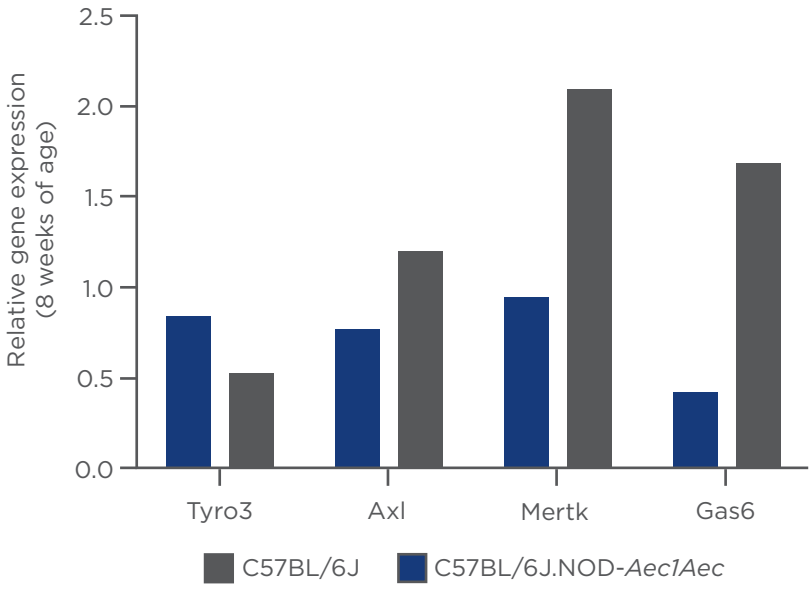


**Figure 1: Differential gene expression of the Tyro3, Axl, and Mertk receptor tyrosine kinase signalling in SjS$^s$-C57BL/6.NOD-*Aec1Aec2* mice.**

Microarray data at 8 weeks of age were presented for C57BL/6.NOD-*Aec1Aec2* and C57BL/6J mice. Hybridisations were carried out with individual RNA samples using Affymetrix GeneChip® Mouse Genome 430 2.0 Array in accordance with the instructions of the manufacturer (Affymetrix, Santa Clara, CA, USA). Microarray data were normalised using the guanine-cytosine robust multi-array average algorithm and analysed using the Linear Models for Microarray Analysis package from the R Development Core Team (The R Project for Statistical Computing) to perform differential expression analyses. B-statistics (the log of the odds of a gene showing either positive or negative trends over time) were calculated for each gene. Genes exhibiting a B-statistic of >1.5 were considered differentially expressed and represents a >82% level of probability that a gene is differentially expressed.
Gas6: growth arrest specific protein 6; SjS: Sjögren's syndrome.

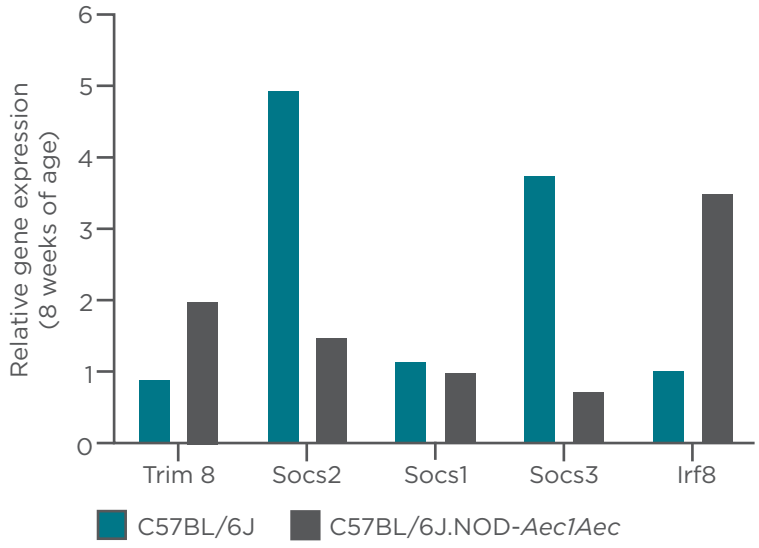


**Figure 2: Differential gene expression of *Socs1* and *Socs3* and their natural inhibitors in SjS$^s$-C57BL/6.NOD-*Aec1Aec2* mice.**

Detailed methodology was described previously.[32,33] In brief, total RNAs were isolated from salivary glands of C57BL/6.NOD-*Aec1Aec2* and C57BL/6J mice at 4, 8, 12, 16, or 20 weeks of age (n=5 per strain per age group). Here, data at 8 weeks of age are presented. Detailed methodology is presented in Figure 1 and elsewhere.[32,33] B-statistics were calculated for each gene. Genes exhibiting a B-statistic of >1.5 were considered differentially expressed and represent a >82% level of probability that a gene is differentially expressed.

In addition to phagocytic activity, TAM RTK receptors and their ligands are directly involved in the suppression of inflammation by physically forming a complex with the IFN-α/β receptor signalling pathway. Humans and animal models of SjS have been shown to express elevated levels of IFN proteins, both IFN-α/β (Type I) and IFN-γ (Type II), as well as multiple IFN-regulated genes, often referred to collectively as IFN-stimulated genes.[31] Earlier studies have indicated that primary SjS patients exhibit an activated Type I IFN system.[51,52] A recent study demonstrated that the Type I IFN signature was highly upregulated in peripheral blood, while Type II IFNs predominated in gland tissues of primary SjS patients.[53] Epigenetic mapping has identified hypomethylation of IFN-regulated genes in whole blood and B cells,[54] and B cell methylation alterations in B cells were more rampant in IFN-regulated gene pathways.[55] Interestingly, Hall et al.[56] have demonstrated that 58% of SjS patients had high IFN activity and these patients were associated with a more severe disease phenotype, in particular focus score. The data suggest that the recruitment of innate cells to the salivary glands leads to high levels of IFNs in response to gland aberration. The inability of TAM receptors to regulate this rapid induction of IFNs potentially results in further gland destruction observed in SjS. Using animal models, Cha et al.[57] revealed that high levels of IFN-γ are detected in mice of the NOD/ShiLtJ and B6.NOD-*Aec1Aec2* lines as early as time of birth, and may suggest a vertical transmission of IFN during pregnancy. In contrast, if these SjS$^s$ mice expressed a non-functional IFN-γ or IFN-γ-receptor encoding gene, they failed to develop any aspect of SjS-like disease, revealing an absolute requirement for IFN-γ in the development and onset of SjS. Further studies by Szczerba et al.[58] and Nandula et al.[59] confirmed that Type I IFN signalling is required for the development of SjS, especially in the development of the glandular pathology. As mentioned earlier, apoptotic cellular debris tends to express PtdSer; it can be recognised directly by the PtdSer receptor or several additional receptors present on phagocytic cells via bridging molecules, including the TAM receptors via Gas6 or Pros1, the integrin molecule αvβ5 via thrombospondin-1, the integrin molecule αvβ3 via the Megf8 molecule, and even the IFN receptor IFN-αR via IFN-α. In addition, phagocytic cells can bind apoptotic debris via CD31 crosslinking, CD36-oxidised low density lipoprotein, and ICAM3 crosslinking. Again, an examination of our

transcriptome database from B6.NOD-*Aec1Aec2* mice indicate that the genes for each of these processes, except the PtdSer receptor, are highly upregulated, as are their downstream signal transduction pathways. The intrinsic inhibition of inflammation following phagocytosis of apoptotic cells is mediated, in large part, by the TAM RTKs present on phagocytic and antigen-presenting cells by interacting with the IFN-αRs. However, the importance of the TAM RTKs in regulating inflammation and self-recognition through the inhibition of innate and adaptive immune responses remains unclear. Nevertheless, there is indirect evidence of a significant role in the TAM RTK-mediated induction of SOCS1 and SOCS3. SOCS1 and SOCS3 normally inhibit the Janus kinase/signal transducers and activators of transcription (STAT) and p130 pathways, respectively, as well as the MyD88 and Trif pathways in toll-like receptor signalling. It is not surprising, then, that the transcriptome data from the salivary glands of C57BL/6.NOD-*Aec1Aec2* mice indicate that neither *Socs1* nor *Socs3* expressions are upregulated, yet their intrinsic regulatory molecules, Trim8 for SOCS1, IRF8 for SOCS3, and SOCS2 for both SOCS1 and SOCS3 each exhibit upregulated gene expressions compared to B6 mice (Figure 2). However, *Socs3* is upregulated, and even co-expressed with the pro-inflammatory cytokine interleukin 17 in SjS patients' peripheral blood mononuclear cells and salivary gland cells, implying that there is a disruption in the normal regulatory activity of the SOCS3 against STAT3. This however reveals a greater complexity in the disease; as patients are usually diagnosed with SjS later in life it is not unlikely that *Socs3*-based regulation could have degenerated over the span of chronic inflammation.

## CONCLUSION

Rheumatic diseases, especially SjS in humans, are characterised by a sustained activation of IFN-stimulated genes during the development and onset of clinical autoimmunity. Under normal circumstances, the IFN signalling pathways, and thereby any subsequent adaptive immune responses, are highly regulated. The lack of regulation results in a dysregulated and activated IFN response. We conceptualise that a series of normal activation-inhibitory interactions at the level of the macrophage during the early innate response to tissue are the underlying cause of development of adaptive autoimmunity leading to SjS.

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# THE RELEVANCE OF HYPERURICAEMIA

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## ABSTRACT

The aim of the present review is to summarise the results from recent clinical studies on the basis of the newly proposed temporal classification of hyperuricaemia and gout, introducing the now evident condition of hyperuricaemia with monosodium urate deposits. Furthermore, it provides an overview of evidence concerning the link between hyperuricaemia and specific pathological conditions, including cardiovascular disease, renal disease, and hypertension.

## INTRODUCTION

Endogenous production of uric acid contributes approximately 75% of the body urate pool, the remainder is derived from dietary intake. Characterised by a limited solubility under physiological conditions, monosodium urate can become prone to crystal formation, an event preferentially occurring within cartilage and fibrous tissues that is facilitated by a reduction in temperature. Different epidemiological and clinical studies also support the role of hyperuricaemia with or without urate deposition as a risk factor for a wide spectrum of non-rheumatological conditions. A range of evidence is available to demonstrate the link between hyperuricaemia with or without urate deposition and a wide spectrum of pathological conditions including arterial hypertension, pulmonary hypertension,[1] renal disease,[2] metabolic syndrome, and cardiovascular disease (CVD).[3-7] This review provides an overview of studies concerning the link between hyperuricaemia and specific pathological conditions, including CVD, renal disease, and hypertension.

## URIC ACID MEASUREMENT AND HYPERURICAEMIA PREVALENCE

When serum uric acid levels are reduced to <6 mg/dL the deposition of uric acid crystals can be prevented, therefore gout management guidelines (i.e. European League Against Rheumatism [EULAR], American College of Rheumatology [ACR]) advise to treat to a target <6 mg/dL in the chronic treatment of the disease.[8,9]

This rising prevalence of hyperuricaemia in recent decades, which is reflected by the concomitant increase of gout incidence, has been ascribed to the Westernisation of diets, malnutrition, and the use of certain medications, mainly including diuretics, acetylsalicylic acid, and ciclosporin, the latter of which is known to reduce the renal clearance of urate.[10,11]

## THE RELEVANCE OF HYPERURICAEMIA FOR CARDIOVASCULAR RISK EVALUATION

Hyperuricaemia with or without urate deposition has been found to be frequently associated with CVD. Indeed, a recent meta-analysis of 35 studies involving almost 100,000 patients showed that hyperuricaemia is a risk factor for incident hypertension.[12] More recently, large amounts of data from the Chinese Cohort Study, involving 93,393 participants (~50% males) demonstrated that hyperuricaemia was an independent risk factor of mortality from all causes, total CVD, and ischaemic stroke. This correlation was more significant

in women than men. This study also found a linear relationship between serum urate (SUA), and all-cause and CVD mortality.[13]

In patients at high risk of CVD, elevated SUA level is an independent predictor of death. For each 1 mg/dL increase of SUA concentration, a rise in the risk of death for all causes of 39% has been reported.[14] The association was stronger in patients with a positive history of coronary artery disease. After adjusting for age, sex, smoking status, alcohol intake, weight, body mass index, waist circumference, blood pressure, history of CVD, estimated glomerular filtration rate (eGFR), cholesterol fractions, and plasma glucose levels, SUA levels continued to be strongly predictive of the risk of death (hazard ratio: 1.26, 95% confidence interval: 1.15–1.38). Prolonged elevation of SUA levels has been found to be associated with peripheral vascular disease, and long-standing elevated SUA levels are predictive of worse outcomes after an acute stroke over 2 years, independently of other comorbidities.[15]

In humans, studies regarding hyperuricaemia and the development of hypertension have generally been consistent, continuous, and of similar magnitude, and epidemiological studies have demonstrated that hyperuricaemia carries an increased relative risk for hypertension within 5 years, independent of other risk factors.[16] Further evidence supporting the pathogenetic role of hyperuricaemia was found in the reduction of both systemic and glomerular pressures occurring with the normalisation of SUA levels provided by febuxostat in rats with oxonic acid-induced hyperuricaemia. Treatment with febuxostat also reduced and alleviated afferent arteriolar thickening, mesangial matrix expansion, and the development of pre-glomerular arteriolar disease. In normal rats, febuxostat lowered SUA levels without any effect on blood pressure, renal haemodynamics, or afferent arteriole morphology.[17]

According to recent hypotheses about the pathogenetic steps in the development of hypertension induced by hyperuricaemia, uric acid has been hypothesised to have a role in driving intracellular oxidative stress, endothelial dysfunction, renin-angiotensin-aldosterone system activation, and reduced nitric oxide (NO) bioavailability (Figure 1).

The intracellular oxidative stress may induce mitochondrial alterations and decrease endothelial NO bioavailability, and also activate the RAS and increase endothelin levels. The net effect is to induce renal and systemic vasoconstriction and the development of hypertension.[18,19] Data from some studies in humans observed that the lowering of urate levels may be beneficial for vascular function by reducing oxidative stress.[20,21]

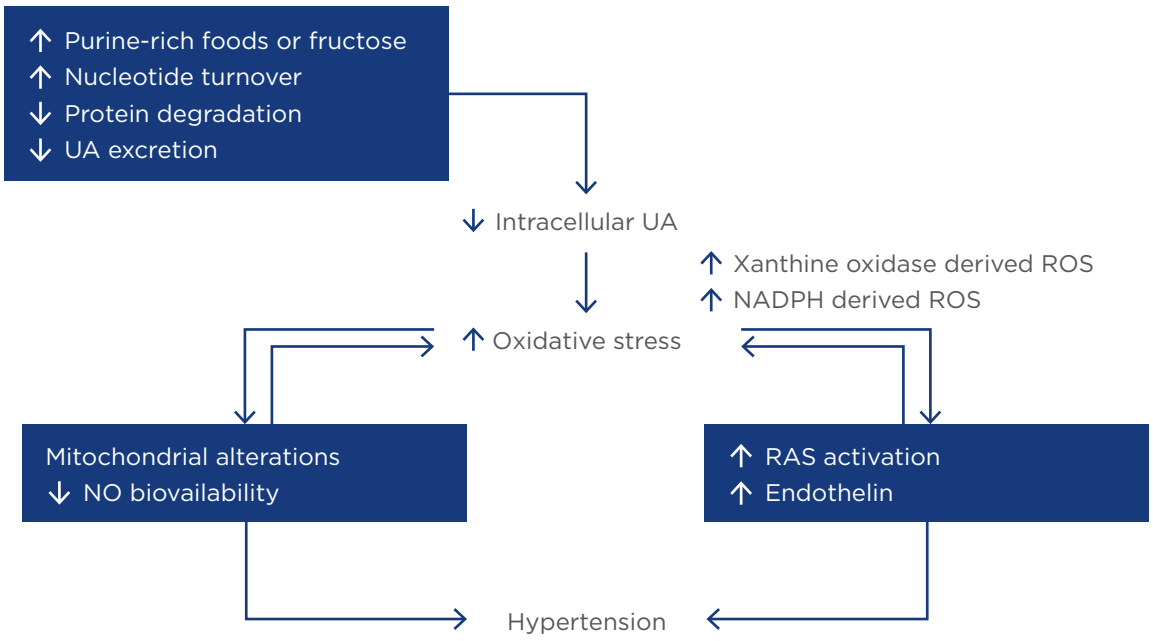


**Figure 1: A model for the explanation of the pathogenetic role of hyperuricaemia in hypertension.**
UA: uric acid; ROS: reactive oxygen species; NADPH: nicotinamide adenine dinucleotide phosphate; NO: nitric oxide.

**Table 1: Change in estimated glomerular filtration rate from baseline by change from baseline serum uric acid.[27]**

| | | Mean Change in SUA from baseline (mg/dL) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ≤3 | | | >3 to ≤4 | | | >4 to ≤5 | | | >5 to ≤6 | | | >6 | | |
| | | n | Mean (95% CI) | SD | n | Mean (95% CI) | SD | n | Mean (95% CI) | SD | n | Mean (95% CI) | SD | n | Mean (95% CI) | SD |
| eGFR (mL/min) | Baseline eGFR | 19 | 67.3 | 15.31 | 17 | 71.1 | 14.07 | 32 | 65.7 | 9.18 | 21 | 67.9 | 13.39 | 26 | 59.5 | 13.10 |
| | Change Year 1 | 19 | -2.2 (-4.8–0.4) | 5.39 | 17 | -0.4 (-5.5–4.8) | 10.02 | 32 | 0.5 (-2.1–3.1) | 7.20 | 21 | -1.4 (-6.4–3.6) | 10.96 | 26 | 2.0 (-1.3–5.3) | 8.19 |
| | Change Year 2 | 11 | -3.6 (-8.7–1.4) | 7.54 | 11 | -4.8 (-9.2– -0.4) | 6.59 | 24 | 2.8 (0.2–5.4) | 6.19 | 18 | -3.7 (-9.1–1.8) | 10.98 | 19 | 4.3 (0.5–8.2) | 8.01 |
| | Change Year 3 | 8 | -4.6 (-11.3–2.1) | 8.03 | 8 | -2.8 (-6.8–1.3) | 4.80 | 22 | -1.5 (-4.6–1.7) | 7.09 | 16 | -6.7 (-14.6–1.3) | 14.90 | 17 | -0.3 (-5.2–4.6) | 9.54 |
| | Change Year 4 | 7 | -8.4 (-18.4–1.5) | 10.77 | 8 | -0.5 (-6.3–5.3) | 6.97 | 21 | -1.7 (-5.5–2.2) | 10.52 | 14 | -2.9 (-6.5–0.8) | 6.40 | 16 | 2.3 (-2.5–7.0) | 8.83 |
| | Change Year 5 | 5 | -10.8 (-19.6– -2.0) | 7.05 | 8 | -2.0 (-7.9–3.9) | 7.01 | 19 | -1.5 (-6.6–3.5) | 10.52 | 14 | 0.6 (-5.7–7.0) | 11.04 | 14 | 0.5 (-4.5–5.5) | 8.59 |

eGFR: estimated glomerular filtration rate; SUA: serum uric acid; CI: confidence interval; SD: standard deviation.

## HYPERURICAEMIA AND CHRONIC KIDNEY DISEASE

More than 50% of patients with gout have some degree of renal insufficiency and nearly 100% had renal disease at autopsy.[16] Large studies like the National Health and Nutrition Examination Survey (NHANES)[22] and the German Chronic Kidney Disease (GCKD) Study[2] show an increase in the incidence of hyperuricaemia in parallel with the decline in eGFR. In addition to this impressive association between impaired renal function, data from 18 prospective cohort studies in 431,000 patients revealed that hyperuricaemia predicts the occurrence of chronic kidney disease (CKD) as well as the rate of decline in renal function.[23] Interestingly, elevated SUA levels have also been found to be an independent predictor of the development of microalbuminuria in diabetes, a surrogate of kidney damage.[24]

### How Does Hyperuricaemia Lead to Renal Damage?

Histopathologic findings in the kidneys of patients with gout are mainly characterised by advanced arteriolosclerosis, glomerulosclerosis, and interstitial fibrosis. It therefore seems that microvascular damage plays an important role in the development of renal impairment due to hyperuricaemia, rather than the classical interstitial nephritis with urate crystal deposition.

Based on data from a large patient population with hyperuricaemia (N=16,186),[25] it was found that subjects achieving SUA <6 mg/dL with urate-lowering therapy are 37% less likely to have renal disease progression. Hence, based on the epidemiological and preclinical data, hyperuricaemia plays an important role in the development of both impaired renal function (decline in eGFR) and of renal damage, i.e. proteinuria. If this paradigm is true, lowering uric acid should have an effect on renal function as well as on renal damage, i.e. proteinuria.

## URATE-LOWERING THERAPY IN CHRONIC KIDNEY DISEASE

The Febuxostat Open-label Clinical of Urate lowering efficacy and Safety (FOCUS) study enrolled 116 hyperuricaemic gout subjects receiving daily doses of febuxostat (40, 80, or 120 mg) for up to 5 years with regular assessment of SUA levels and eGFR. In this cohort of patients a *post hoc* analysis clearly demonstrated the correlation between maintenance or improvement in eGFR and the quantitative reduction in SUA levels from baseline. For every 1 mg/dL decrease in SUA concentration, the model projected an expected

improvement in eGFR of 1 mL/min from the untreated value.[26] These results were further confirmed by an analysis of two Phase III studies, considering the subjects who received only febuxostat throughout the duration of the studies (n=551). Greater sustained decreases in subjects' SUA levels were associated with a smaller decline in renal function (p<0.001), as shown in Table 1.[27]

A consensus document for the detection and management of CKD published by the Spanish Scientific Societies reported that in patients with symptomatic hyperuricaemia and mild-to-moderate renal failure, febuxostat administration had demonstrated greater efficacy and a similar safety to allopurinol, without the need to adjust the dose.[28]

## CONCLUSIONS

Hyperuricaemia has been found to be associated with a wide spectrum of non-rheumatological conditions. Results of several animal and human studies have clearly demonstrated the link between hyperuricaemia with or without deposition and a wide spectrum of pathological conditions, including CVD, arterial hypertension, pulmonary hypertension, and CKD.[7]

The life-long risk of developing gout has been reported to arise with SUA concentration above 6 mg/dL, which represents the limit rationally proposed for a definite, evident, and universally accepted definition of hyperuricaemia. Lowering SUA levels could produce cardiovascular and renal benefits. This appears likely to be related to the overproduction of reactive oxygen species and vascular inflammation sustained from increased SUA levels (blood vessels) as well as increased renin production and reduced NO levels with interstitial fibrosis and inflammation (kidney).

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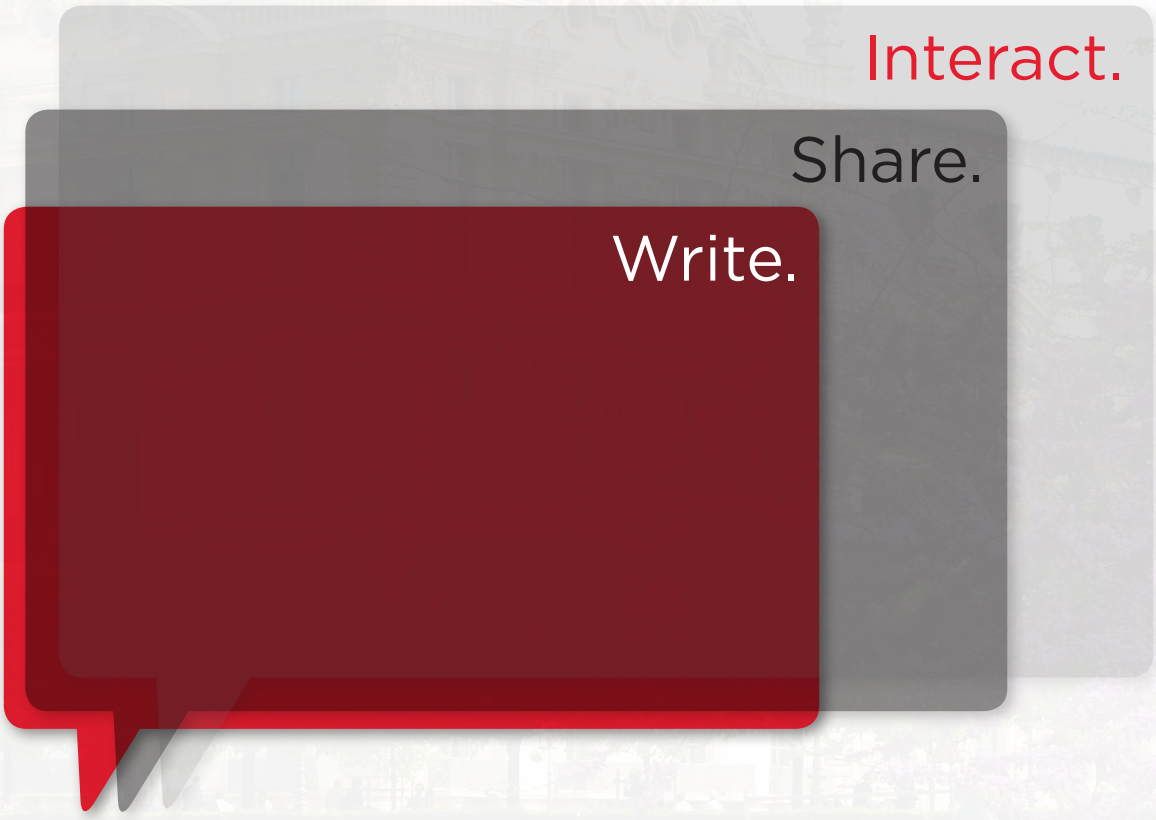


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# NON-INVASIVE CARDIOVASCULAR IMAGING FOR CARDIOVASCULAR RISK ASSESSMENT IN RHEUMATOID ARTHRITIS

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## ABSTRACT

People with rheumatoid arthritis (RA) are often under-recognised as a group with elevated risk of cardiovascular (CV) disease and increased morbidity from CV events. Standard clinical risk assessment tools, which take into account traditional CV risk factors such as smoking, diabetes, hypertension, hyperlipidaemia, and family history do not accurately predict CV risk in patients with autoimmune rheumatic disorders; therefore, there is an unmet need for other methods to assess their risk. Non-invasive CV imaging is evolving as a novel clinical tool to determine subclinical atherosclerotic coronary artery disease in patients with RA. Non-invasive imaging studies, such as tests of endothelial function (i.e. reactive hyperaemia index and flow-mediated dilation) and arterial stiffness (i.e. pulse-wave velocity), have been identified as a potential means for providing accurate assessment of early CV risk in the general population and are evolving in their utility for patients with RA. These types of non-invasive imaging have the potential to eliminate the current use of invasive assessments for identification of precursors to coronary artery disease, such as coronary angiography for early endothelial cell dysfunction. By combining the expertise of subspecialists in cardio-rheumatology clinics, the expectation is to pre-emptively identify RA patients with early coronary artery disease, allowing early modification of risk factors through either medical management or lifestyle modification.

Keywords: Cardio-rheumatology, endothelial cells, flow-mediated dilation (FMD), aortic pulse-wave velocity (aPWV).

## INTRODUCTION

Rheumatoid arthritis (RA) is a common inflammatory autoimmune condition presenting in a symmetrical fashion in both large and small joints, and is defined by the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria as definite clinical synovitis in ≥1 joint and a score ≥6 in four domains: number/site of involved joints, serological abnormality, elevated acute phase response, and symptom duration of at least 6 weeks. The epidemiology of RA varies by geographic region and by ethnic/racial group with 1% of the worldwide population affected; RA develops in women 2 to 3-times more often than men, with the lifetime risk of RA being 3.6% in women and 1.7% in men.[1]

People with RA have increased mortality attributable to atherosclerotic cardiovascular disease (ASCVD) events,[2] and a 1.5 to 2-fold increased risk of developing ASCVD compared with the general population. A recent meta-analysis identified a 50% increased risk of death in patients with RA compared with the general population,[3,4] and at the time of RA diagnosis, patients in the study were >3-times as likely as the general population to have had a prior myocardial infarction. Standard CV risk assessment scores have been shown to markedly underestimate the risk of CV disease events in the RA population. In one study, the observed

CV risk was 2-fold higher in female RA patients than the Framingham Risk Score predicted, and was 65% higher in men.[4] The Reynolds Risk Score (which includes C-reactive protein [CRP]) was similarly deficient in estimating the risk.[4] While a heightened risk of CV events exists in patients with RA, we have yet to uncover an accurate method for estimating that risk. Lack of such knowledge is an important problem, given the poor survival rate and heightened mortality from ASCVD in patients with RA compared with the general population.

## CARDIO-RHEUMATOLOGY

Cardio-rheumatology is an emerging field addressing the unmet clinical and research needs of identifying early atherosclerosis in patients with rheumatic disease.[2] These unmet needs include identification of silent, or 'subclinical', atherosclerosis, inability to predict CV risk in RA patients based on the traditional CV risk scores, and understanding the role of inflammation.[2] The use of non-invasive CV imaging for CV risk assessment is of interest in the field of cardio-rheumatology, and has been encouraging in its ability to detect early atherosclerosis and endothelial dysfunction in RA patients, thus enhancing the co-ordination of care of RA patients between cardiologists and rheumatologists.[2,3] Ideally, through the early identification of CV risk by non-invasive CV imaging, cardiologists will assist rheumatologists in the modification of risk factors in RA patients.

The typical presentation of CV symptoms is often under-recognised in patients with inflammatory autoimmune disease, and classic symptoms of cardiac angina and myocardial infarction often go unrecognised in RA patients.[5] Patients with RA are twice as likely as the general population to develop silent myocardial infarctions and sudden cardiac death, and receive less regular counselling for other traditional risk factors such as smoking, hypertension, and maintaining healthy activity levels.[2,3,5] As reviewed by Crowson et al.,[3] chronic glucocorticoid use, visceral adiposity, low muscle mass, elevated risk of venous thromboembolism, and low activity levels from debility are also important cardiac risk factors in RA patients. In persons with RA, early intervention for modifiable CV risk factors and recognition of subclinical accelerated atherosclerosis is desperately needed. Crowson et al.[3] found that only 55% of patients with RA in one study had lipid levels measured; management by rheumatologists was associated with less frequent lipid screening, showing that patients with RA generally have less primary and secondary preventative screening.[3,5] The hope of the joint endeavours in cardio-rheumatology clinical practice is to ameliorate the heightened morbidity from CV disease, and identify other non-invasive methods to assess CV risk that are different from the traditional risk scores.

## CHALLENGES TO ASSESSING CARDIOVASCULAR RISK IN RHEUMATOID ARTHRITIS

The accelerated and diffuse nature of subclinical atherosclerosis in patients with autoimmune disease is comparable to patients with diabetes mellitus; however, traditional risk factors (male sex, smoking, family cardiac history) seem to play a greater role in ASCVD associated with diabetes mellitus, whereas systemic inflammation appears to have greater significance in RA.[2] Patients with RA have greater underlying inflammation and lower lipid levels in comparison with the general population, exemplifying the many challenges in CV risk stratification and pharmacologic prevention in patients with autoimmune disease.[3] Lipid levels therefore have a paradoxical relationship with CV risk in RA patients, because lower lipid levels are typically associated with more severe systemic inflammation, which is associated with enhanced CV risk.[3] Statins (hydroxymethylglutaryl coenzyme A reductase inhibitors) appear to reduce vascular inflammation and have been tested for efficacy in the treatment of RA, but they present challenges in the RA patient because of drug interactions.[6] It is considered that statins may have a beneficial effect on endothelial function, arterial stiffness, and in improving high density lipoprotein-cholesterol anti-inflammatory properties in patients with RA.[3,5] Rollefstad et al.[6] performed an observational study using non-invasive imaging with carotid ultrasound within a cardio-rheumatology preventative clinic. Four hundred and twenty-six patients with inflammatory joint disease (257 RA, 108 ankylosing spondylitis, and 61 psoriatic arthritis) were stratified for subclinical CV risk using the systematic coronary risk evaluation (SCORE), which also included a bilateral carotid artery ultrasound to assess for the presence of plaque.

**Table 1: Comparison of traditional and modified cardiovascular risk scores.**

| Prediction variables | Framingham (Revised 2008) | Reynolds CVD risk score for men 2008 | QRISK® and QRISK®2 | ACC/AHA pooled cohort hard CVD risk calculator | SCORE CVD death risk calculator 2003 | ATP III hard CHD risk score 2002 |
|---|---|---|---|---|---|---|
| Age | x | x | x | x | x | x |
| Gender | x | | x | x | x | x |
| Total chol | x | x | x | x | x | x |
| HDL chol | x | x | x | x | x | x |
| Systolic BP | x | x | x | x | x | x |
| DM | x | | | x | | |
| Current smoking | x | x | x | x | x | x |
| BP treatment | x | | x | x | | x |
| Family Hx CVD | | | x | | | |
| Parental history of MI before age 60 years | | x | | | | |
| Region of Europe | | | | | x | |
| Region of United Kingdom | | | x | | | |
| BMI kg/m$^2$ | | | x | | | |
| Serum hs-CRP | | x | | | | |

HDL: high density lipoprotein-cholesterol; BP: blood pressure; DM: diabetes mellitus; Family Hx: family history; CVD: cardiovascular disease; MI: myocardial infarction; BMI: body mass index; hs-CRP: high sensitivity C-reactive protein; chol: cholesterol; CHD: coronary heart disease; SCORE: Systemic Coronary Risk Evaluation; ATP: Adult Treatment Panel; ACC: American College of Cardiology; AHA: American Heart Association.

Typical CV risk factors included smoking status, diabetes mellitus, family history of premature CV disease, and patient history of peripheral vascular disease or transient ischaemic attack. In this study, 36.6% of patients had a SCORE <5%, and therefore did not require lipid lowering management, although half of the study population was identified as having plaque present on carotid ultrasound. The remainder of the study patients (n=270) went on to be treated with primary or secondary prevention with statin medication in accordance with guideline-recommended lipid targets. Even though several patients with inflammatory joint disease in the study had established coronary artery disease, many were not using lipid lowering treatment at the time of referral to the study, illustrating the need for improved CV risk factor management in patients with RA.[6] The Rollefstad et al.[6] study illustrates that one of the goals of the cardio-rheumatology collaboration is to modify the risk factors for ASCVD in RA patients with early recognition by including non-invasive imaging, such as carotid ultrasound, with the goal of initiating early therapy.[2,3,5,6] Although the heightened CV risk has been recognised in RA patients for several decades, providers are often hesitant to prescribe statin drugs for this population due to the concern of exacerbating myalgias and arthralgias. This study provides further evidence of the necessity of early statin drug initiation in this patient population.[6]

**Table 2: Comparison of non-invasive cardiovascular imaging methods.[22]**

| Imaging methods | FMD | Brachial artery US | CIMT | aPWV | Aix |
|---|---|---|---|---|---|
| Arterial ultrasonography | x | x | x | | |
| Arterial tonometry | | | | x | x |
| Expensive | | x | | | |
| Requires operator skill | | x | | | |
| Early changes able to be identified? | x | | x | | |
| Measure of arterial stiffness? | | | | x | x |
| Measures of vascular age? | | | x | | x |
| Acts as a surrogate for atherosclerotic disease burden? | | | x | | |
| Biomarker for endothelial function | x | | | | |
| Microvascular function | | x | | | |

FMD: flow-mediated dilation; US: ultrasound; aPWV: aortic pulse-wave velocity; Aix: aortic augmentation index; CIMT: carotid intima media thickness.

## REVIEW OF TRADITIONAL AND MODIFIED CARDIOVASCULAR RISK SCORES

A current limitation in identifying CV risk in patients with RA is that the degree of subclinical coronary atherosclerosis in patients with rheumatic disease is substantially under-recognised by current CV risk assessment scores, therefore making it difficult to pre-emptively identify RA patients who have a higher CV risk. Incidence of ASCVD events in patients with RA is underestimated by the CV scoring systems developed for use in the general population, such as the Framingham, Reynolds, American Heart Association/American College of Cardiology (AHA/ACC), and European Risk Scores, and QRISK®2 risk calculator (Table 1).[4] The Framingham Risk Score is designed for the general population anddoes not predict CV events accurately in patients with RA.[4] As reflected in the JUPITER (Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial, it is notable that markers of acute phase response such as CRP are often elevated in RA patients, and are known risk markers for heart disease in the general population.[7] However, even with CRP taken into account using the Reynolds Risk Score, the risk of CV disease in patients is underestimated. Persons with RA are at a 1.5 to 2-fold increased risk of developing CV disease compared with the general population, a 2-fold risk of myocardial infarction, and a 10-year risk of CV events is 60% higher than that in the general population.[4] A recommendation by EULAR was that the traditional CV risk scores (Framingham) be multiplied by 1.5 in patients with RA (i.e. those who have disease duration of 10 years, positive rheumatoid factor [RF], or anti-citrullinated protein antibodies), to reflect their true risk of heart disease. However, implementation of the 1.5 multiplier failed to identify 88% of patients with carotid intima media thickness >0.9 mm and carotid plaques.[8] In fact, these modified traditional risk scores continue to underestimate ASCVD, especially in patients with older age, positive RF, and persistently elevated erythrocyte sedimentation rates and CRP levels.[9] Further studies have sought to identify other ways of assessing CV risk, andrecent developments through the use of non-invasive CV imaging studies, with a focus on endothelial dysfunction and arterial stiffness, have been fruitful (Table 2).[4]

## ATHEROSCLEROSIS AND ITS SURROGATE MARKERS FOR CARDIOVASCULAR DISEASE

In autoimmune diseases, accelerated ASCVD occurs from an interplay of pro-inflammatory cytokines, immune and endothelial cell dysfunction, and general upregulation of adhesion molecules that remains incompletely understood.[2] In RA, chronic inflammation is known to be a key factor in escalating early atherosclerosis. Prasad et al.[2] discussed the activation of the nuclear factor kappa B pathway by interleukin-6, tumour necrosis factor alpha (TNF-α), and pro-inflammatory cytokines, causing enhanced leukocyte permeation and activation that leads to accelerated atherosclerosis. Interestingly, patients with RA have lower lipid levels in periods of severe systemic inflammation, and patients with autoimmune disease have been found to have higher levels of oxidised low density lipoprotein.[2,3] As reviewed by Crowson et al.,[3] these factors can lead to a decrease in apolipoprotein A1 and diminished high-density lipoprotein atheroprotective effects, which may result in enhanced ASCVD. Finally, the significance of RF and anti-citrullinated protein antibody-positivity in patients with rheumatic disease, and the relationship that these auto-antibodies play in affecting ASCVD is unclear.

## ENDOTHELIAL DYSFUNCTION AS A PRECURSOR TO CORONARY ARTERY DISEASE

Coronary endothelial dysfunction exists in most patients with coronary artery disease, and is associated with adverse CV events.[10] Endothelial activation and dysfunction are precursors to atherosclerosis.[10,11] While traditional CV risk factors continue to be evaluated in clinical practice to predict the likelihood of atherosclerotic disease, non-invasive imaging methods that assess endothelial function in patients with early atherosclerosis to predict CV risk are in development.[10] Normal endothelium, which lines the vascular circulatory system, is a 'complex organ' with the purpose of vascular homeostasis, and it maintains an atheroprotective role through vasodilation and inhibition of platelet aggregation.[11] Reduction in levels of nitric oxide, an endothelium-derived vasodilator, results in endothelial dysfunction.[10] Nitric oxide mediates arterial vasodilation in response to shear stress caused by arterial flow. Cardiac catheterisation is an invasive method used for evaluating coronary endothelial function by using infusions into the peripheral vessels (like acetylcholine into the brachial artery); it is considered to be the gold standard invasive assessment of endothelial function.[10,11] The responses indicated by venous occlusion plethysmography, which measures volume change in the forearm, assume that endothelial dysfunction is both generalised and systemic, and can be used to establish if there is generalised endothelial dysfunction.[10,11] Endothelial dysfunction is proven to be reversible with aggressive lifestyle interventions such as weight loss, physical activity, smoking cessation, pharmacologic medications like anti-hypertensives, and statin use. Identification of endothelial dysfunction may thus help identify early coronary artery disease in patients with inflammatory diseases such as RA, and provide opportunities to initiate lifestyle modification.[9,10]

## STUDIES OF NON-INVASIVE ARTERIAL HEALTH ASSESSMENTS

Non-invasive CV imaging methods to assess the diffuse and systemic nature of endothelial function are promising, and are based on characterising the atherogenic and atheroprotective function of the endothelium.[10] These methods include reactive hyperaemia peripheral arterial tonometry (RH-PAT) and flow-mediated vasodilation (FMD) (Table 2).[10-12] RH-PAT measures peripheral endothelial cell function using finger probes to measure pulse-wave amplitude at rest and during reactive hyperaemia.[12] This method employs the use of digital pulsatile volume changes, correlating with endothelial cell dysfunction, and is unique in that it reflects microvessel vasodilation.[13] Digital pulse volume is affected by levels of nitric oxide and therefore also depends on endothelial function.[10,12,13] Another non-invasive assessment, forearm FMD, is a biomarker of endothelial dysfunction that measures the diameter of the brachial artery at rest and during reactive hyperaemia, which is achieved by the release of a blood pressure cuff around the patient's arm after being inflated to above-systolic pressure for a few minutes and employing high resolution ultrasound imaging to assess the brachial artery endothelial function.[10,11] This artery is used due to ease of access, and the percentage of FMD is computed using the following formula:

(maximum diameter-baseline diameter)/baseline diameter x 100.[14]

Use of FMD to assess endothelial dysfunction was evaluated by Fichtlscherer et al.[15] when they studied patients with angiographically confirmed coronary artery disease, and assessed endothelial function 8 weeks after an episode of acute coronary syndrome, showing improvement in endothelial function. Likewise, Hamburg et al.[16] showed that abnormal FMD in a large community-based sample was also associated with elevated age, blood pressure, and higher body mass index, thus showing correlation between endothelial dysfunction and traditional CV risk factors. Bonetti et al.[12] investigated the relationship between RH-PAT in patients without obstructive coronary artery disease by performing RH-PAT and coronary angiography on the same day in 94 patients, and found that the RH-PAT index was higher in patients with normal coronary endothelial function, and was significantly lower in patients with endothelial dysfunction. This study revealed that RH-PAT could be an efficient non-invasive test to identify individuals with coronary endothelial dysfunction.[12]

## FLOW-MEDIATED DILATION IN RHEUMATOID ARTHRITIS

With respect to RA, FMD has been used as a non-invasive assessment to show evidence of impaired conduit artery endothelial function. Typically, the finding of a higher FMD is associated with higher levels of inflammation; therefore, the percentage of FMD is higher in RA patients with high levels of disease activity. With respect to levels of disease activity, Watanabe et al.[14] evaluated 25 patients with RA who met the ACR 1987 revised criteria, and showed that the percentage of brachial FMD correlated with patients that had higher disease activity, as measured by the 28-joint disease activity score, DAS28. This study confirmed that a higher percentage of FMD correlated with higher inflammation, and therefore higher disease activity scores.[12]

The effects of RA treatment, such as traditional disease modifying anti-rheumatic drug (DMARD) therapy (methotrexate) and TNF inhibitors, have been assessed for their effect on measures of FMD.[17] Hansel et al.[17] hypothesised that switching from DMARD therapy to anti-TNF-α inhibitor therapy in patients with low disease activity would modify endothelial function. They tested vascular function at the endothelial level after infusing acetylcholine into the brachial artery at graded doses and measured forearm blood flow by a calibrated strain gauge plethysmograph.[17] This study demonstrated an impairment of endothelium-dependent vasodilation in young patients with a prolonged history of RA and low disease activity. This is interesting, because the results were obtained during a period of low inflammatory activity of the disease, and presence of endothelial dysfunction indicates endothelial damage from sustained cytokine stress. The study by Watanabe et al.[14] also echoed these findings, concluding that using anti-TNF therapies, such as infliximab, etanercept, and adalimumab correlated with the percentage of FMD in randomly selected RA patients, in addition to disease activity as mentioned previously. The percentage of FMD increased significantly in the group treated with anti-TNF therapy compared with the group treated with DMARD (methotrexate, bucillamine, and sulfasalazine) therapy, demonstrating that TNF inhibition improves endothelial function in patients with RA.[14] Vaudo et al.[18] showed that RA patients with low disease activity but without clinically obvious atherosclerotic disease or traditional CV risk factors have a lower mean brachial FMD compared with control subjects, as measured by non-invasive ultrasound. This study also identified that there was no difference in measures of brachial artery FMD in patients that had a positive RF or erosive disease.

## PULSE-WAVE TRANSMISSION

Another marker of subclinical atherosclerosis is increased arterial stiffness, where the arterial wall becomes thickened and loses its elasticity due to chronic inflammation. Pulse pressure, which is one measure of arterial stiffness, can assess risk for adverse CV events. Widening of the pulse pressure, occurring when the systolic blood pressure increases and/or diastolic blood pressure decreases, is associated with heightened CV mortality. Large arteries, such as the aorta, have a constant transmission of the arterial pressure through the arterial wall, which is influenced by the elastic properties of that wall; the velocity of this pulse-wave transmission (PWV) is a measure of arterial stiffness (Table 2). The stiffer the artery, whether from age-related changes, or atherosclerotic disease, causes an increase of PWV. Aortic PWV, which measures the rate

at which aortic pressure waves travel, is a non-invasive method to assess arterial stiffness, an independent predictor of CV risk.[13] It is performed by use of a tonometry probe to compress the patient's radial artery, recording multiple waveforms in sequence, and using computer software that analyses the average central waveform, providing a measure of aortic augmentation index (Aix).[13] Klocke et al.[13] evaluated the Aix as a measure of arterial stiffness in 14 RA patients with no cardiac disease and found that the mean Aix was higher in the RA group than the control group, but interestingly did not correlate with DAS28 scores. This suggests that Aix may be a sensitive marker for early CV disease in patients with RA and provides a non-invasive assessment tool to assess CV risk. Malik et al.[19] and Kullo et al.[20] investigated the association of forearm microvascular and brachial artery function assessed by brachial artery ultrasound, with measures of PWV to assess central arterial stiffness in subjects with subclinical coronary artery disease. Their findings of higher resting shear stress with greater pulse pressure and aortic PWV suggest that elevated shear stress in the brachial artery may be a marker of greater arterial stiffness. Ambrosino et al.[21] conducted a systemic review and meta-analysis which showed that more severe inflammation in patients with RA caused significantly higher aortic PWV, even in the early stages of RA.

## CONCLUSION

People with RA have higher case fatality after an acute myocardial infarction than the general population, with higher morbidity from subclinical CV disease. Well-known CV risk assessment tools, such as the Framingham or Reynolds Risk Scores, do not accurately predict CV risk in patients with RA. Given the increased risk of premature atherosclerosis, aggressive control of traditional risk factors is particularly important in patients with inflammatory joint disease and early identification of subclinical atherosclerotic disease using novel non-invasive CV risk assessment tools such as FMD, RH-PAT, and aortic PWV is promising. The widespread screening of patients with RA for endothelial dysfunction is not currently recommended due to limited supporting data on the efficacy of these tools, small size of research investigations, lack of standardisation of tools, and potential cost. Nonetheless, these novel imaging tools are promising as a means of identifying patients with RA and other rheumatic diseases who are at increased risk of ASCVD. Future research will determine if non-invasive cardiac imaging to identify subclinical atherosclerotic disease is a cost-effective approach to diminish mortality risk in patients with rheumatic diseases.

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# PSORIATIC ARTHRITIS: A REVIEW

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## ABSTRACT

Psoriatic arthritis is an inflammatory arthritis which affects the skin and musculoskeletal system. If not diagnosed early and treated effectively it can result in joint deformity and disability. Treatments such as oral disease modifying anti-rheumatic drugs and biologic therapy are effective but have side effects which could limit their use in certain individuals. Further research aimed at identifying cases earlier in order to improve outcomes is currently being conducted.

Keywords: Psoriatic arthritis (PSA), disease modifying anti-rheumatic drugs (DMARDs), biologics, the classification of psoriatic arthritis (CASPAR), dactylitis, arthritis mutilans, rheumatoid arthritis, tumour necrosis factor alpha (TNF-α).

## INTRODUCTION

Psoriatic arthritis (PSA) is a chronic condition which can cause considerable disability and pain if not recognised and treated properly. Approximately 15% of patients affected by psoriasis will develop associated joint disease.[1] It was first recognised in 1964 and is now considered part of the spondyloarthropathy (SPA) group of diseases.[1] PSA can cause significant joint deformity, and can also affect the surrounding structures of joints such as tendons and ligaments. Research has shown that there is associated cardiovascular comorbidity. However, treatments have now been developed which can control the disease and achieve remission.

It is important that PSA is recognised early in order to be effectively treated. There is evidence that a proportion of PSA patients remain undiagnosed.[1] Although in most cases patients develop arthritis after having had psoriasis, there is a group of patients that develop joint symptoms prior to any skin manifestations, causing confusion and delay in diagnosis. Research has been focussed on developing scoring systems and diagnostic criteria which can identify such cases at an early stage.

## GENETIC FACTORS

Psoriasis and PSA are strongly heritable conditions[2,3] when compared with other inflammatory rheumatic conditions. Family history of psoriasis/PSA (or other features of the SPA spectrum such as inflammatory bowel disease and iritis) can provide strong support for the diagnosis of PSA when assessing a patient suspected of having the disease.[3] PSA is thought to be more heritable than psoriasis.[1] Different human leukocyte antigen alleles are associated with PSA.[1] Certain gene polymorphisms are also more strongly associated with PSA, including tumour necrosis factor alpha (TNF-α) promoter, major histocompatibility complex class 1, and some interleukin (IL) receptors. The pattern of inheritance is complex and multigenic and varies from dominant in some families to recessive in others.[3]

## PATHOPHYSIOLOGY

It is still not clear what exact mechanism lies behind the development of PSA. It is thought to be multifactorial and secondary to environmental, genetic, and immunological factors.[1] Over-activation of the immune system when triggered in the skin and joints causes an inflammatory cascade,

resulting in signs such as scaly skin plaques and joint synovitis in those individuals who are genetically susceptible. The synovitis which is detected in PSA can be pathologically different to that found in rheumatoid arthritis (RA).[3] In PSA the synovitis resembles more of a SPA type, with high numbers of neutrophils and greater vascularity when compared with the RA synovitis, thus suggesting that PSA is a separate condition from RA both genetically and pathologically.

Bone changes in PSA are thought to be secondary to osteoclast proliferation which are activated by cytokines. These changes include erosions, osteolysis, and new bone formation.[1] Inflammation in PSA can also affect surrounding tissue such as ligaments and tendons, which is more uncommon in RA. Inflammatory cells infiltrate the entheseal and ligament tissues causing subsequent pain and swelling. Imaging studies have shown that joint capsules and tenosynovial tissues can also be affected by inflammation in PSA. Thus in clinical assessment, it is important to focus on other sites of inflammation and not just concentrate on how many tender or swollen joints the patient has.

Pro-inflammatory cytokines such as TNF-α are present in psoriatic plaques and synovial fluid in large amounts.[1] TNF-α is also found in many other arthropathies and biologic drugs which are aimed at blocking TNF-α have been effective therapies for such conditions. Although they are useful in PSA, other therapies such as the B cell-depleting rituximab is not as effective in PSA when compared with RA.[3] Thus there are still distinct cell lines that are unique to the inflammation found in PSA and which need further research for therapeutic purposes. In particular, T helper cell 17, IL-17, and IL-23 are inflammatory mediators which have a significant role in the disease process of PSA, and research is aimed at targeting these cells.

## CLINICAL FEATURES

PSA is considered an inflammatory arthritis and part of the SPA group of diseases. Its clinical features can vary from causing mild joint pains to presenting as a rapidly erosive debilitating illness causing lasting joint damage. It can affect both the axial and peripheral joints, commonly presenting in an oligoarticular pattern. Two features which are hallmarks of PSA are the presence of dactylitis and enthesitis.

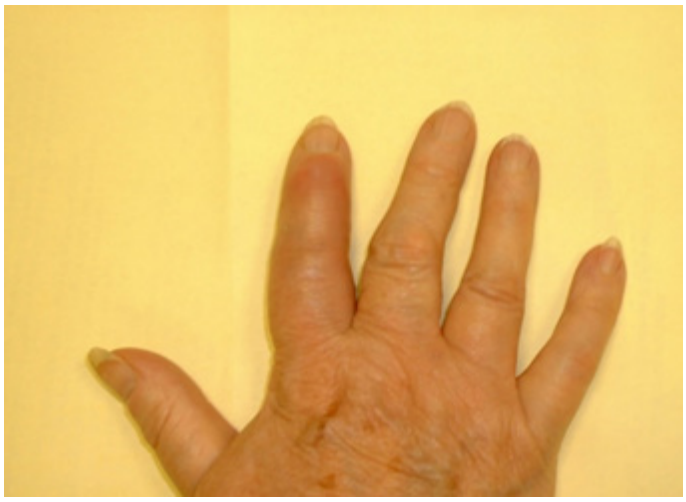

**Figure 1: Patient presenting with dactylitis.**

Dactylitis is inflammation of an entire digit (Figure 1). It can affect up to 40% of patients with PSA.[4] It occurs secondary to inflammation of the digital flexor tendon sheaths. Some studies have shown that it is associated with erosive joint damage. It commonly occurs in the feet; most often in the fourth toe. The presence of dactylitis could indicate overall disease severity.[4] Enthesitis is inflammation of tendon/ligament insertions into the joint,[5] and is a common feature of PSA and the other SPAs. Patients are usually tender over the tendon insertion sites in the elbows, heels, and iliac crest. The achilles tendon is most commonly affected.

Patients with PSA can also develop extra-articular signs, most frequently in the nails. The close anatomical association between the nail and the distal interphalangeal joint is perhaps why the nail is so often affected in PSA.[6] Typical changes include nail pitting and onycholysis. Splinter haemorrhages and hyperkeratosis can also occur. Nail pitting can be used as part of diagnostic criteria for PSA. If PSA is left untreated then it can lead to a condition known as arthritis mutilans. This manifests as a shortening of the digits with severe osteolysis,[7] and can cause considerable pain and discomfort for the patient. It can also result in significant functional disability.

### Classification for Psoriatic Arthritis (CASPAR) Criteria

Scoring systems have been developed to try and identify PSA at an early stage and criteria have been developed to aid in classification of the

disease from the other SPAs and inflammatory arthritides. Not only are they useful for identifying PSA earlier, they can also help identify cases of PSA which do not present in the typical manner. Some criteria include PSA with the SPA group. The classification for psoriatic arthritis (CASPAR) criteria was developed specifically for PSA.[1] It has good sensitivity and specificity for those presenting with disease of <2 years' duration.[1] Although primarily used for classification, it can be used for diagnostic purposes.[8]

The CASPAR criteria consists of established inflammatory articular disease (joint, spine, or entheseal) with at least three points from the following features:

a) Current psoriasis (assigned a score of 2; all other features are assigned a score of 1): skin or scalp disease as evidenced by a rheumatologist or dermatologist
b) A personal history of psoriasis (unless current psoriasis is present): can be obtained from any healthcare professional
c) A family history of psoriasis (unless current psoriasis is present or there is a personal history of psoriasis): first or second degree relatives
d) Current dactylitis or history of dactylitis recorded by a rheumatologist
e) Juxta-articular new bone formation: as evidenced on radiographs
f) Rheumatoid factor negativity: can be by any laboratory method
g) Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis

## INVESTIGATIONS

A diagnostic test for PSA does not exist[3,9] unlike in RA which is cyclic citrullinated peptide and rheumatoid factor positive. As in other inflammatory conditions, markers such as erythrocyte sedimentation rate and C-reactive protein can be raised in PSA. Immunoglobulin A can be elevated in a proportion of patients. Joint aspirate can be inflammatory, with an increase in white cell count and polymorphs.[9]

Radiographic changes can be more diagnostic of PSA and help to differentiate it from other inflammatory arthropathies. As well as bony erosions, other signs on radiography include ankyloses, joint space narrowing, and osteolysis.[3] The 'pencil-in-cup' deformity is characteristic of PSA.[3] It results from peri-articular erosions leading to the appearance of a pencil in a cup, most often affecting the distal interphalangeal joints. Bony growths over tendon and ligament attachments can also be seen. However, it is important to note that these changes can be non-specific[3] and are not present in all patients.

Further imaging such as magnetic resonance imaging (MRI) can help to identify soft tissue involvement in further detail, particularly when a patient is suffering from enthesitis.[10] Ultrasound has also become a useful tool in the investigation of arthritis; it can help to identify bony erosions in those patients where synovitis or dactylitis is not always evident clinically. Studies have shown that ultrasound scan and MRI are more sensitive for detecting inflammation than plain radiographs in PSA.

## TREATMENT

As discussed, PSA can be debilitating for the patient if not adequately treated. Fortunately, treatments have been developed which can help to halt disease progression and maintain function for the individual affected, as well as alleviate any pain the patient may suffer from. A multidisciplinary approach between rheumatology and dermatology is often necessary in order to maximally treat the condition.[11]

Corticosteroids are used in PSA and in many other inflammatory arthropathies in order to provide immediate symptom relief. They can rapidly diminish the inflammatory response seen in these conditions, causing a reduction in swelling and stiffness in the joints. They can be given as an intramuscular injection for general widespread relief or directly injected into the affected joint for a more targeted response.[1] Long-term steroid use should be avoided due to the side effect profile which includes diabetes, hypertension, osteoporosis, and immunosuppression. There is also a risk of skin psoriasis flares after intramuscular injections.[12] In most cases steroids are used for short-term relief and occasionally as bridging therapy while establishing the patient on more long-term immunosuppressants.

Disease modifying anti-rheumatic drugs (DMARDs) are used in PSA as in other inflammatory conditions. They are a group of drugs which can help to reduce inflammation as well as to slow disease progression to prevent joint damage, as opposed to nonsteroidal anti-inflammatory drugs

and steroids which treat the inflammation but not the underlying cause. However, evidence behind their use in PSA is not as robust as in RA. Use of DMARDs is mostly based on a clinician's experience rather than evidence.[1] Methotrexate can cause improvement in both the skin and peripheral joints. Sulfasalazine is useful for peripheral arthropathy although only with weak evidence. Cyclosporine has beneficial effects on the skin. Small studies have shown that leflunomide has similar efficacy for use in PSA as compared with RA. The main side effect with DMARDs is their immunosuppression, which can expose the patient to potentially serious infections such as neutropenic sepsis. Methotrexate also commonly causes nausea and gastrointestinal disturbance which can be severe and unpleasant. Liver function has to be closely monitored with methotrexate and leflunomide due to the risk of liver toxicity.

Biologic therapies that have been developed in the last 20 years have been shown to be effective treatments for inflammatory conditions. Some biologics target TNF-α, a pro-inflammatory cytokine, which is involved in both the skin and joint manifestations of the disease. These drugs are expensive and are usually used when other therapies have failed. In most cases treatment failure would be considered when patients have failed two or more DMARDs used in combination and still have evidence of active disease. Biologics have been proven to reduce disease activity and improve quality of life, but their side effects include increased risk of infection, reactivation of tuberculosis, worsening of congestive cardiac failure, and demyelination syndromes.

## Emerging Therapies

Recently ustekinumab has been licensed for PSA.[1] It is a human monoclonal antibody which blocks a signalling pathway in the disease by preventing IL-12 and IL-23 from binding to IL-12Rβ1. In addition, apremilast, a new oral, targeted, synthetic DMARD has been licensed, which targets phosphodiesterase 4. Apremilast offers a number of advantages over conventional DMARDs such as low toxicity and lack of monitoring need, but its efficacy in practice has yet to be fully evaluated. Further studies are researching other cytokines that can be targeted such as IL-17.[1]

## SUMMARY

PSA is a complex autoimmune disorder which affects a number of sites within the body. Clinically distinct from RA, significant advances have been made in understanding the pathogenesis of the disease and a number of therapies have been shown to be effective treatments. However, a diagnostic test for the condition still does not exist, and further research is being conducted in order to develop a robust diagnostic model which can be used to identify and treat PSA as early as possible, as well as to develop new therapies.

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# THERAPIES IN THE PIPELINE FOR SYSTEMIC AUTOIMMUNE DISEASES

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## ABSTRACT

The current goals in the development of novel therapeutics of systemic autoimmune diseases are to develop agents more effective than conventional therapies as well as to reduce the risk of organ damage. To achieve this goal, large multicentre randomised controlled trials are needed to confirm the efficacy and safety of novel agents. Whether these novel modalities are synergistic to conventional drugs, the optimal dosages, and duration of treatment, need to be explored.

As expected, the development of new molecules for the treatment of autoimmune diseases is constant, and there are different ongoing clinical trials. We review the different molecules in the pipeline, summarised in Tables 1, 2, and 3. We also show the successes, failures, and molecules that require more evidence.

Keywords: Systemic lupus erytematosus (SLE), Sjögren's syndrome (SS), anti-phospholipid syndrome (APS), new therapies.

## SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disease of unknown aetiology, with unpredictable disease course intermingled with periods of remission and exacerbation.[1,2] For decades, therapy for SLE has been based on glucocorticosteroids, hydroxychloroquine, and immunosuppressive agents leading to an improvement in the prognosis of the disease. However, the occurrence of refractory disease and adverse events related to conventional therapies still represents a challenge.[3] The immunopathogenesis of SLE is complex with dysregulation of T helper Type 1, 2, and 17 pathways that results in the elevation of the levels of a number of pro-inflammatory cytokines such as tumour necrosis factor alpha, interleukin (IL)-6, 10, 15, 18 and interferon (IFN)-α in patients with active SLE.[3]

### B Cell Therapies

B cells can be selectively targeted for depletion either via direct B cell molecules such as CD19, CD20 (rituximab and ocrelizumab), and CD22 (epratuzumab) or by inhibition of B cell survival factors: B lymphocyte stimulator (BLyS) (belimumab, tabalumab, blisibimod) and a proliferation-inducing ligand (APRIL) (atacicept).[3]

The use of rituximab in patients with SLE has been investigated in two randomised controlled trials (RCT): the EXPLORER study (Exploratory Phase II/III SLE Evaluation of Rituximab)[4] in patients with moderate-to-severe extra-renal SLE receiving immunosuppressants and corticosteroids, and the LUNAR study[5] in patients with proliferative lupus nephritis (LN) treated concomitantly with mycophenolate mofetil (MMF) and corticosteroids. These studies failed to demonstrate additional benefit and superiority of rituximab, respectively. Despite these results, rituximab is still extensively

used 'off-label', especially in refractory cases to standard treatment, in light of 'experience-based' medicine and their use is included in the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) recommendations for refractory LN.[3,6,7]

## Belimumab

The efficacy and safety of belimumab was tested by two pivotal RCT, BLISS-52[8] and BLISS-76,[9] that included 1,684 SLE patients with mild-to-moderate disease activity (excluding severe renal or central nervous system involvement). In both studies a dose of 10 mg/kg plus standard treatment met the primary efficacy endpoint: a greater SLE responder index (SRI) index atb Week 52. *Post hoc* analyses of the two BLISS trials found that patients that had a SELENA-SLEDAI score ≥10, with low complement, were anti-dsDNA positive, or had baseline corticosteroid use, demonstrated greater response.[10]

**Table 1: New therapies in the pipeline for systemic lupus erythematosus.**

| Therapy | Target | Clinical stage for SLE treatment | Primary result |
|---|---|---|---|
| **B cell depletion** | | | |
| Rituximab | CD20 | Off-label label use, LUNAR (N=144) and EXPLORER (N=257) Phase II/III | LUNAR: renal response rates 56.9% for RTX and 45.8% for placebo (p=0.18)<br>EXPLORER: no difference in major/partial clinical responses, overall response rate 28.4% versus 29.6% for placebo and RTX, respectively |
| Ocrelizumab | CD20 | Phase III BEGIN and BELONG (N=381) trials | BEGIN: interrupted early, no benefit to patients with active SLE<br>BELONG: stopped due to increased serious infections, mainly ocrelizumab+MMF |
| Epratuzumab | CD22 | Phase II trials ALLEVIATE 1 (N=14) and 2 (N=90) and EMBLEM (N=227), Phase III EMBODY 1 and 2 trials | ALLEVIATE 1 and 2: improved rates of BILAG, terminated due to disruption in drug supply<br>EMBLEM: improved rates of BICLA, higher proportion of responders in all groups than placebo |
| **Blockade of B cell cytokine activation** | | | |
| Belimumab | BAFF | Approved pivotal trials BLISS 52, BLISS 76 | Greater SRI index at Week 52 |
| Belimumab | BAFF | Phase III for LN | |
| Atacicept | BAFF/ APRIL | Phase II/III APRIL-SLE (N=461), APRIL-LN (N=6) | APRIL-SLE: 150 mg dose beneficial effects versus placebo in flare rates and time to first flare, reduced total Ig levels, anti-dsDNA, increased complement<br>APRIL-LN: terminated prematurely, unexpected reduced IgG and serious infections |
| Blisibimod | Anti-B-Lys | Phase II PEARL-SC (Phase III: CHABLIS-SC1 on course) | Improved SR-5, reduced proteinuria, reduced anti-dsDNA and B cells, increased complement |
| Tabalumab | Anti-B-Lys | Phase III ILLUMINATE 1 (N=1,164) and 2 trials (discontinued due to lack of efficacy) | ILLUMINATE I: no significant improvement SRI-5 Week 52, secondary endpoints did not meet.<br>ILLUMINATE 2: higher dose only met primary endpoint |
| **Blockade of T cell co-stimulation** | | | |
| Rigerimod | | Phase IIB (N=136) | Higher SRI than placebo Week 12 (62 versus 39) |
| Abatacept | CTLA4 | Phase IIB (N=118) | Failed to meet the primary/secondary end-point (new flare/BILAG) |
| Edratide | | Phase II (N=340) | Failed to achieve co-primary endpoints: SLEDAI-2K and adjusted mean SLEDAI |
| CDP7657 | CD40L | Phase I (N=17) | 100% patients with mild AE, moderate intensity, two serious AE |
| AMG 557 | ICOS: B7RP1 | Phase I NCT00774943 | |
| MEDI-570 | ICOS | Phase I NCT01127321 | Terminated (business reasons) |
| JAK116439 | JAK | Phase II | |

**Table 1 continued.**

| Therapy | Target | Clinical stage for SLE treatment | Primary result |
|---|---|---|---|
| **Cytokine-directed therapy** | | | |
| Tocilizumab | IL-6 | Phase I (N=16) (RCT are awaited) | Improvement in SLEDAI score >4 in 53% patients, reduction in anti-dsDNA |
| Sirukumab | IL-6 | Phase I (N=46) II | Phase II: fails improve proteinuria. Interrupted due high infection rates |
| Laquinimod | IL-6, 12, 17 and 23, TNF-α | Phase IIa (N=46) | Additive effect with MMF and CS, improve renal function and proteinuria |
| Rontalizumab | IFN-α | Phase II ROSE study (N=159) | Reduced IFN signature, BILAG and SRI were similar between rontalizumab and placebo groups. *Post hoc*: improvement signs and symptoms, flare rates, steroid burden Week 24 |
| Sifalimumab | IFN-α | Phase IIb (N=431) | Reduced SRI-4 at Day 365, clinical improvements skin, joint, and patient-reported outcomes |
| Anifrolumab | IFN-R | Phase II (N=305) | Reduced SRI-4 at Day 365, steroid sparing, lower rates of BILAG |
| AMG-811 | IFN-γ | Phase I (N=21) | Reduction levels CXCL10 (IP-10) levels and IFN-γ, improvement proteinuria |
| IFN-α kinoïd | IFN-α | Phase I/II (N=28) | Higher anti-IFN-α titres in signature-positive patients, and C3 levels |
| AGS-009 | IFN-α | Phase Ia (N=28) | Safe and well tolerated, no signficant neutraliztion of IFN signture at doses >0.6 mg/kg |
| **Fcy receptor modulation** | | | |
| SM101 | FcyRIIB | Phase IIa (N=51) | SRI-4 response rate was twice as high in the SM101-treated patients versus placebo, response in patients with LN was greater, improvement skin and arthritis |
| **Toleragen molecule** | | | |
| Abetimus sodium | Anti-dsDNA | Phase II/III ASPEN trial (N=890) | Reduced anti-dsDNA. Not meet the expected endpoint. Study stopped |
| **Proteasomes** | | | |
| Bortezomib | Proteasome inhibitor | Phase II (N=12) (7 patients discontinued) | Disease activity decline and remained stable for 6 months. AE: 17 |

SLE: systemic lupus erythmatosus; RCT: randomised controlled trials; IL: interleukin; TNF: tumour necrosis factor; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SRI: SLE Responder Index; AE: adverse effects; BICLA: BILAG-based Combined Lupus Assessment; BILAG: British Isles Lupus Assessment Group; CS: corticosteroids; IFN: interferon; Ig: immunoglobulin; IP-10: interferon gamma-induced protein 10; LN: lupus nephritis; MMF: mycophenolate mofetil; RTX: rituximab; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

## Ocrelizumab

Two Phase III RCT, the BEGIN and renal BELONG, investigated the efficacy of ocrelizumab in non-renal and renal SLE, respectively.[11] The BEGIN study was interrupted early because ocrelizumab was not likely to benefit patients with SLE. The BELONG trial recruited patients with proliferative LN (Class II/IV), treated them with high dose steroids, and either MMF or cyclophosphamide.[12] A total of 381 patients were recruited before the trial was terminated due to an imbalance of the rate of adverse effects; 233 patients passed the 32-week point and the difference was nonsignificantly higher than placebo (67% versus 55%).

## Epratuzumab

Early studies with epratuzumab in SLE included two small trials (ALLEVIATE-1 and ALLEVIATE-2)[13] which compared two treatment arms with epratuzumab (360 mg/m$^2$ or 720 mg/m$^2$) and

a placebo arm. Although after 12 weeks of treatment, patients who had received treatment with epratuzumab improved in British Isles Lupus Assessment Group (BILAG) indices, these trials were interrupted prematurely due to a lack of drug supply. Recently, the EMBLEM[14] Phase IIb trial was published. This study included 227 patients with SLE who were assigned to six different arms: one placebo arm and five arms with varied doses of epratuzumab. The results of this study (BILAG responses after 12 weeks of treatment) suggested that epratuzumab could be effective in the treatment of SLE, for this reason two Phase III trials (EMBODY 1 and 2) are ongoing.[15,16]

## Tabalumab

The ILLUMINATE trials include two Phase III trials evaluating the efficacy and safety of tabalumab. In ILLUMINATE-1 the primary endpoint, the SRI-5 response, was not met for either dose group (120 mg once every 2 weeks [Q2W] and 120 mg once every 4 weeks) at Week 52. Statistical significance was not achieved on secondary measures of clinical efficacy, despite the observed biological response.[17] In ILLUMINATE-2 the primary endpoint was met in the 120 mg Q2W group but the secondary endpoint was again not met.[18] Collectively, these data did not meet expectations for efficacy in the context of existing treatments, leading to discontinuation of the development of tabalumab for SLE.

## Blisibimod

Blisibimod is a fusion protein between the fragment crystallisable region domain of one immunoglobulin (Ig)G and four B cell activating factor (BAFF) binding domain peptides, that selectively binds to BLyS. The efficacy and safety of subcutaneous blisibimod was evaluated in the Phase IIb trial PEARL-SC in 547 patients with SLE.[19] The SRI-5 was higher in the patients randomised to the highest dose of blisibimod 200 mg once weekly compared to placebo, reaching statistical significance at Week 20 (p=0.02). This response was higher in patients with SLEDAI improvements ≥8, and in the subgroup of patients with SLEDAI ≥10 at baseline. A significant reduction in proteinuria was observed in subjects with a protein to creatinine ratio of 1:6 at baseline. Their biological effect was evidenced by the normalisation of biomarkers of SLE activity: decrease in anti-dsDNA (p<0.01) and increase in complement C3 (p<0.01) and C4 (p<0.001). These encouraging results have led to the evaluation of the effects of blisibimod through ongoing Phase III trials (CHABLIS-SC1-NCT01395745).[20]

## Atacicept

Atacicept is a recombinant fusion protein consisting of the TACI receptor that binds both BLyS and APRIL fused with the fragment crystallisable region portion of IgG; neutralising both BLyS and APRIL might be more effective than BLyS alone. In Phase Ib studies with different dose regimens the biological activity of atacicept was observed, with dose response reduction of B lymphocytes and immunoglobulin levels, particularly IgM, followed by the IgA and IgG.[21] A later Phase II/III RCT of two doses of atacicept (75 mg or 150 mg) was designed to assess whether it could prevent flares in patients treated with corticosteroids. Two fatal infections occurred in the atacicept arm of 150 mg leading to premature termination of this group, but in this group a significant reduction in the flare rate (43% versus 60%; odds ratio [OR]: 0.49 [0.26–0.92], p=0.027) and a delayed time to first flare compared to placebo (hazard ratio [HR]: 0.56 [0.36–0.87], p=0.009) were observed.[22] Based on the fact that APRIL could be a potential biomarker for predicting hard-to-treat cases of LN, a Phase II/III RCT was initiated to evaluate their efficacy and safety in patients with active LN who recently started corticosteroids and MMF. An unexpected decline in serum IgG and serious infections occurring in six patients led to early termination of the trial.[23] These results suggest that the dose of concurrent immunosuppressive medications should be reduced.

## Targeting the Interferon

The key role of IFN-α in lupus has been substantiated by transcriptome analysis in which the upregulation of numerous IFN-α dependent genes in peripheral blood mononuclear cells from lupus patients was reported, constituting an overall 'IFN signature' in SLE. This signature is present in 50–80% of SLE patients.[24] There is promising preclinical evidence that the inhibition of the secretion and downstream effectors of both IFN-α and IFN-γ may be effective for the treatment of SLE. The primary agents that are currently in development are monoclonal neutralising antibodies that bind to and neutralise IFN-γ (AMG 811), IFN-α (sifalimumab, rontalizumab, and

AGS 009) or its receptor (anifrolumab [ANIFR]), and IFN-α-kinoid.[24]

## Anifrolumab

The efficacy and safety of ANIFR were assessed in a Phase II RCT in SLE patients (N=305) stratified by SLEDAI score, corticosteroid dose, and IFN gene signature (IFN high versus IFN low). Patients were randomised to receive ANIFR (300 mg, 1,000 mg) or placebo.[25] The primary endpoint, SRI-4 response at Day 169, was met by a greater proportion of ANIFR-treated patients (placebo: 17.3%; 300 mg: 34.3%, p=0.014; 1,000 mg: 28.8%, p=0.063). Corticosteroid reduction to ≤7.5 mg/day at Day 365 was achieved by 26.6% of placebo, 56% of 300 mg (p=0.001), and 31.7% of 1,000 mg (p=0.595) patients. At Day 365, the secondary SRI endpoint was met by 51.5% of the patients taking a 300 mg dose of ANIFR (p>0.001), 38.5% of those taking a 1,000 mg dose (p=0.048), and 25.5% of those taking a placebo. A persistent benefit across multiple global and organ-specific measures was also demonstrated, as well as lower rates of BILAG moderate/severe flares.

**Table 2: New therapies in the pipeline for primary Sjögren's syndrome.**

| Drug | Target | Clinical stage for pSS treatment | Primary result |
|---|---|---|---|
| Hydroxychloroquine | IFN inhibition | JOQUER trial Phase III RCT (N=120) | No score improvement by at least 30% on two of the three VAS (dryness, pain, and fatigue) at Week 24. No significant difference between the two groups in any of the secondary clinical endpoints: ESSPRI, ESSAI, Schirmer's test, salivary flow, Ig levels, SF-36, PROFAD, SSI, HAD |
| **B cell depletion** | | | |
| Rituximab | CD20 | TEARS (N=120) | No sustained score improvement by at least 30% on two of the four VAS (dryness, pain, fatigue, and global) |
| | | TRACTISS (N=133) | No improvement by at least 30% on oral dryness and fatigue, no improvement on overall dryness, ESSAI, lacrimal flow, QoL; improved unstimulated salivary flow |
| Epratuzumab | CD22 | Open label (N=16) | Improved Schirmer's test, unstimulated salivary flow, and VAS fatigue score |
| Belimumab | BLISS | Open label (N=30) | 60% of patients responded, with a decrease in the ESSDAI without change in salivary flow or Schirmer's test; a significant decrease in Ig levels and RF was also observed |
| Abatacept | | Open label (N=11) ASAP trial (N=15) | Reduced glandular inflammation, reduced number of lymphocytic foci and numbers of local FoxP3 T cells Increased saliva production Reduced ESSDAI and ESSPRI, reduced RF IgG levels, reduced fatigue, increased QoL |
| Tocilizumab | IL-6 | ETAP trial RCT Phase II/III (N=110 estimated enrolment) NCT01782235 | To evaluate: improvement ≥3 points of the ESSDAI score |
| Baminercept | Lymphotoxin-β | Phase II RCT (N=72 estimated enrolment) NCT01552681 | To evaluate: change in stimulated whole salivary flow |

pSS: primary Sjögren's syndrome; ESSDAI: Sjögren's syndrome Disease Activity Index; ESSPRI: EULAR Sjögen's syndrome Patient Reported Index; HAD: hospital anxiety and depression; IFN: interferon; Ig: immunoglobulin; PROFAD: profile of fatigue and discomfort; QoL: quality of life; SF-36: 36-item Medical Outcomes Study Short Form Health Survey; SSI: Sicca Symptoms Inventory; VAS: Visual Analogue Scale; RCT: randomised controlled trial.

The lack of dose response was likely due to the fact that even the lower dose suppressed ~90% of activity in 21 IFN-regulated genes. At present, ANIFR's Phase II results outpace sifalimumab, which had smaller effect sizes. If the results hold, ANIFR could become the second new drug to treat SLE in more than 50 years.

## SJÖGREN'S SYNDROME

Sjögren's syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands and usually presents as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands.[26] B lymphocytes are some of the key therapeutic targets, either directly or indirectly by inhibiting IFN, BAFF, IL-6, or IL-21.[27] Symptomatic and topical treatments are essential in most patients with limited glandular disease; systemic immunomodulatory treatments must be used in patients with extra-glandular manifestations, occurring in one-third of the patients.[28]

### Interferon Inhibition

According to the new insights into its pathogenesis, SS is considered an innate immune-triggered epithelitis resulting from the activation of toll-like receptors, IFN pathways, and B and T lymphocytes.[29] Hydroxychloroquine is the only IFN inhibitor evaluated in SS[30] and is usually prescribed for patients with fatigue, arthralgia, and myalgia, rather than severe systemic manifestation. Evidence regarding its efficacy is limited, with data derived from open retrospective studies and one crossover trial.[31-34]

To clear this issue, the JOQUER trial, a multicentre RCT was conducted in 120 SS patients.[35] Patients were randomised (1:1) to receive hydroxychloroquine (400 mg/day) or placebo until Week 24. The primary endpoint was the improvement at 24 weeks by ≤30% of two of the three patient visual analogue scales (VAS) of the most frequent symptoms: dryness, pain, and fatigue. No efficacy was observed for this endpoint. In addition, there was no significant difference between the two groups in any of the secondary clinical endpoints, or in systemic disease activity assessed by the EULAR SS disease activity index (ESSDAI). There was no efficacy in patients with anti-Ro autoantibodies, high IgG levels, or systemic involvement.[35]

### B Cell Targeted Therapies

Several B cell molecules can be targeted. CD20, CD22, and the BAFF are potential targets for strategies designed to modify B cell function in SS, both directly and indirectly.[36,37] The most widely studied target for achieving B cell depletion is the CD20 antigen. Observational studies as well as open-label studies and registries have shown that rituximab is effective in SS patients with active disease and extra-glandular disease, improving both subjective and objective complaints including salivary function, with an observed overall efficacy in up to 60% of the patients.[38]

In two small RCT, rituximab showed a significant improvement from baseline on fatigue, the stimulated whole saliva flow-rate, and several other variables (e.g. B cell and rheumatoid factor [RF] levels, unstimulated whole saliva flow rate, lacrimal gland function, multi-dimensional fatigue inventory scores, Short Form 36 health survey scores, and VAS scores for sicca symptoms).[39,40]

To assess if rituximab can be used in large populations of patients and if it changes the course of the disease, two large double blind studies were undertaken. The TEARS study (Tolerance and Efficacy of Rituximab in primary Sjögren's syndrome) which included 120 patients having either recent and active disease and/or at least one extra-glandular severe involvement, was recently published.[41] The primary endpoint was the improvement in 6 months of at least 30 mm of two of the four patient VAS: pain, fatigue, dryness, and disease activity. At Week 6, the proportion of patients with improvement in the primary endpoint was significantly higher in the rituximab group, without sustained significant improvement at 24 weeks. Showing that rituximab does not appear to relieve symptoms of SS, at least in the short-term.[41]

The other trial, TRACTISS study (Anti-B-cell therapy in patients with primary Sjögren´s syndrome), the largest randomised trial of biologic therapy in SS, included 133 patients to receive rituximab or placebo.[42] The primary endpoint was the improvement in VAS scores of fatigue and oral dryness. Secondary outcomes were VAS scores for fatigue or oral dryness separately, global assessment of SS activity, pain, ocular and overall dryness, as well as salivary and lachrymal flow rates, quality of life, and ESSDAI. In this trial there was no improvement of symptoms in the rituximab

arm; the response rates were 39.8% and 36.8% in the placebo arm (adjusted OR: 1.13, 95% confidence interval [CI]: 0.50–2.55). In addition, there were no significant differences in any outcome measure, except unstimulated salivary flow.[43]

## Epratuzumab

In an open-label study, 16 SS patients (14 women, 2 men) were scheduled to receive four epratuzumab infusions at 2-week intervals. The most commonly improved parameters were Schirmer's test, unstimulated whole salivary flow, and VAS fatigue scores. A clinical response was noted in 53% of patients at 6 weeks and 67% at 32 weeks. Epratuzumab is not currently approved for the treatment of any autoimmune diseases and no double blind studies are currently planned in SS to confirm these data.[44]

## B Cell Activating Factors in Sjögren´s Syndrome

BAFF transgenic mice develop autoimmune-like manifestations reminiscent of SS as they age: enlarged salivary glands, severe sialadenitis, and decreased production of saliva.[45,46] Histological analysis of salivary glands reveals numerous features also present in human SS: the formation of germinal centres (GC) and ectopic GC.[46] In SS, BAFF provides anti-apoptotic signals and their expression may be increased in lymphoma.

**Table 3: New therapies in the pipeline for antiphospholipid syndrome.**

| Treatment | Target | Clinical stage for APS treatment | Primary result |
|---|---|---|---|
| **Direct oral anticoagulants** | | | |
| Rivaroxaban | Factor-Xa inhibitor | Phase II/III RAPS (N=156) with/ without SLE, on warfarin target INR 2.5 for previous VTE (on course)<br>Phase III RCT TRAPS (N=536) triple positive patients with APS (on course) | Non-inferior to warfarin, pending results |
| Hydroxychloroquine | Annexin A5 resistance | Observational 12 week (unknown) NCT01475149 | Change in annexin V resistance assay |
| | Inhibition of toll like-receptors | Phase III APS ACTION trial (N=75) NCT02635126 | Changes in the number of acute thrombosis (arterial or venous) |
| **B cell inhibition** | | | |
| Rituximab | CD-19 | RITAPS trial (N=19) | Safe, does not change aPL profiles, effective in controlling some but not all non-criteria manifestations: skin ulcers, aPL, cognitive dysfunction, nephropathy, thrombocytopenia |
| **Complement inhibition** | | | |
| Eculizumab | Terminal complement protein C5 | Phase II (N=10) renal transplanted patients with history of CAPS NCT01029587<br>Mouse models | Prevention of CAPS after kidney transplant attenuates thrombosis in mouse models of APS, prevents pregnancy loss |
| Sirolimus | mTORC (anti-phospholipid syndrome nephropathy) | Observational (N=10) | aPL IgG stimulated mTORC through PI3K-AKT pathway, patients treated with sirolimus showed no recurrence of vascular lesions and had decreased vascular proliferation, 70% functioning renal allograft 144 months after transplantation versus 11% untreated<br>Activation of mTORC was found in vessels of autopsy specimens from patients with CAPS |

APS: antiphospholipid syndrome; aPL: antiphospholipid antibodies; CAPS: catastrophic antiphospholipid syndrome; VTE: venous thromboembolism; mTORC: mammalian target of rapamycin; IgG: immunoglobulin G; SLE: systemic lupus erythematosus; INR: international normalised ratio.

BAFF antagonists may be used in the treatment of SS. Patients with hypergammaglobulinaemia, autoantibody production, ectopic GC, and lymphomas would be candidates for this therapy.[46]

An open-label trial, the BELISS, included 30 patients who were treated with belimumab. The primary endpoint, assessed at Week 28, consisted of obtaining at least two of the following five response criteria: VAS reduction ≥30% of dryness, fatigue, pain, or systemic activity, and reduction >25% in serum levels of some markers of B cell activation. They found that 60% of the patients (18/30) responded to belimumab with a decrease in the ESSDAI, but had no change in salivary flow or Schirmer's test. A significant decrease in Ig levels and RF was also observed.[47] Therapy with belimumab also induced a significant reduction in transitional and naïve B cell subsets to levels similar to those observed in healthy donors, normalised BAFF-R expression in all subsets in the memory compartment, with a decrease in the levels of Ig, RF, and anti-nuclear antibodies, and an increase in the C4 complement fraction.[48]

### Inhibition of T Cell Co-Stimulation

In SS, T lymphocytes represent the majority population of salivary infiltrate. Given the recognised role of T cells and B cells in SS, selective modulation of co-stimulation represents a rational therapeutic strategy. The first open trial of abatacept in 11 patients with SS significantly reduced glandular inflammation and induced several cellular changes: a decrease of the number of lymphocytic foci and numbers of local FoxP3 T cells, with an increase of saliva production. However, the clinical effects were not standardised by clinimetric measures (ESSDAI, EULAR SS patient-related outcomes [ESSPRI], and fatigue).[49]

Another open-label study, the ASAP trial, was performed in 15 SS patients. A significant reduction of disease activity (measured by ESSDAI and ESSPRI) was observed and laboratory parameters such as the RF and IgG levels were lowered during treatment with abatacept. Fatigue also improved and patients experienced better health-related quality of life. The function of the salivary and lacrimal gland did not change during treatment.[50]

## ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is an autoimmune disorder characterised by venous and arterial thrombosis and recurrent fetal losses, frequently accompanied by a moderate thrombocytopenia, and the presence of persistent circulating antiphospholipid antibodies (aPL).[51] The main goal of clinical management in APS is to avoid thrombotic and/or obstetric complications. Long-term anticoagulation with an oral vitamin K antagonist (VKA) constitutes the cornerstone of the pharmacological approach to thrombotic APS. A recent report issued by the task force on aPL stated that VKAs remain the mainstay of anticoagulation in APS and that direct oral anticoagulants may be considered in APS patients with a first or recurrent venous thromboembolisation occurring off or on sub-therapeutic anticoagulation, only when there is known VKA allergy/intolerance or poor anticoagulant control.[52] There is a growing number of case series where direct oral anticoagulants have been used in APS with varying degrees of success and failure. Successes were achieved in one series in which rivaroxaban was used for secondary prevention in patients with previous deep vein thrombosis, labile international normalised ratio (INR), simplification of the anticoagulation regimen and no triple aPL positivity patients.[53-55] Failures had the common denominator of presence of either recurrent thrombosis, arterial thrombosis, autoimmune disease, triple antibody positivity, or non-thrombotic manifestations of the disease, constituting patients with the highest risk profile.[56-58] Two large-scale ongoing studies clarify this issue, the first: the Rivaroxaban in Antiphospholipid Syndrome (RAPS) trial,[59] involving patients with a similar profile to those who were successful with rivaroxaban treatment. If this study demonstrates that the anticoagulant effect of rivaroxaban is not inferior to that of warfarin in absence of/less adverse effects, this would provide sufficient supporting information to change the practice, making rivaroxaban the standard of care for the patients with APS with or without SLE who have venous thromboembolism requiring an INR target of 2.5 in first instance. The second: the Rivaroxaban in Thrombotic Antiphospholipid Syndrome (TRAPS)[60] trial will include patients with predictors of failure including triple aPL-positive patients with clinical manifestations of APS, arterial events, and/or pregnancy morbidity, and so is portending less promising results.

Despite the pathogenic role in thrombosis of aPL, therapy should not primarily be directed at effectively reducing the aPL levels. To date

this can be accomplished by several regimens, including high dose steroid administration, immunosuppression, or plasma exchange. This elimination is temporary as antibodies return on cessation of therapy and the use of immunotherapy is generally not indicated unless required for the treatment of the underlying condition, e.g. SLE, or in acute life-threatening situations such as the catastrophic APS.

The management of aPL-positive patients with or without APS is currently suboptimal due to the anticoagulation not being fully effective, the limited knowledge of the specificity, and biological activities of aPL, new drug development for aPL-positive patients is challenging. Perhaps in the future the antithrombotic approach in APS patients may be replaced by a potentially safer immunomodulatory approach.[52]

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# IDIOPATHIC INFLAMMATORY MYOPATHIES: ASSOCIATION WITH OVERLAP MYOSITIS AND SYNDROMES: CLASSIFICATION, CLINICAL CHARACTERISTICS, AND ASSOCIATED AUTOANTIBODIES

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## ABSTRACT

Idiopathic inflammatory myopathies (IIM) are traditionally identified as a group of disorders that target skeletal muscle due to autoimmune dysfunction. The IIM can be divided into subtypes based on certain clinical characteristics, and several classification schemes have been proposed. The predominant diagnostic criteria for IIM is the Bohan and Peter criteria, which subdivides IIM into primary polymyositis (PM), primary dermatomyositis (DM), myositis with another connective tissue disease, and myositis associated with cancer. However, this measure has been criticised for several reasons including lack of specific criteria to help distinguish between muscle biopsy findings of PM, DM, and immune-mediated necrotising myopathy, as well as the lack of identification of cases of overlap myositis (OM). Because of this issue, other classification criteria for IIM have been proposed, which include utilising myositis-associated antibodies and myositis-specific antibodies, as well as overlap features such as Raynaud's phenomenon, polyarthritis, oesophageal abnormalities, interstitial lung disease, small bowel abnormalities such as hypomotility and malabsorption, and renal crises, amongst others. Indeed, the identification of autoantibodies associated with certain clinical phenotypes of myositis, in particular connective tissue disease-myositis overlap, has further helped divide IIM into distinct clinical subsets, which include OM and overlap syndromes (OS). This paper reviews the concepts of OM and OS as they pertain to IIM, including definitions in the literature, clinical characteristics, and overlap autoantibodies.

Keywords: Polymyositis (PM), dermatomyositis (DM), overlap myositis (OM), overlap syndromes (OS), scleroderma.

## OVERVIEW OF IDIOPATHIC INFLAMMATORY MYOPATHIES

Idiopathic inflammatory myopathies (IIM) are traditionally identified as a group of disorders that target skeletal muscle due to autoimmune dysfunction. The IIMs can be divided into subtypes based on certain clinical characteristics, and several classification schemes have been proposed. Overall, the IIMs are characterised by common laboratory and clinical features including: proximal muscle weakness, elevation of muscle enzymes, characteristic muscle biopsy pathology, electromyography findings of inflammatory myopathy, and insertional irritability. Typical skin rashes, including heliotrope rash and Gottron's papules, are associated with dermatomyositis (DM). The predominant diagnostic criteria for IIM is the Bohan and Peter (B and P) criteria, which subdivides IIM into primary polymyositis (PM), primary DM, myositis with another connective tissue disease (CTM), and myositis associated

with cancer (CAM).[1,2] This criteria has however been criticised for several reasons including lack of specific criteria to help distinguish between muscle biopsy findings of PM, DM, and immune-mediated necrotising myopathy,[3] as well as the lack of identification of cases of overlap myositis (OM). As a result of this issue, other classification criteria for IIM have been proposed, including a clinico-serologic classification put forward by Troyanov et al.,[2] which utilises myositis-associated antibodies (MAA) and myositis-specific antibodies (MSA), and also includes overlap features.

According to this criteria, subsets of IIM are divided into PM, DM, and OM, which includes features such as Raynaud's phenomenon, polyarthritis, oesophageal abnormalities, interstitial lung disease (ILD), small bowel abnormalities such as hypomotility and malabsorption, and renal crises, among others. Indeed, the identification of autoantibodies associated with certain clinical phenotypes of myositis, in particular CTM overlap, has further helped divide IIM into distinct clinical subsets. For example, there are now >15 CTM overlap auto antibodies that have been identified.[4] In general, OM has been described as having features of myositis overlapping with clinical features of systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA).[5] Certain autoantibodies in particular may be more significant in association with OM, including anti-PM/Scl, anti-U3RNP, anti-Ku, and the anti-synthetase antibodies.[4-10] In addition, certain end-organ associations, including cardiac, lung, and kidney involvement, are more likely to be relevant clinical manifestations of OM. However, despite the widespread use of the term OM, there appears to be no set consensus as to how this entity is optimally defined.

## HISTORICAL EVOLUTION OF IDIOPATHIC INFLAMMATORY MYOPATHIES CLASSIFICATION OVER TIME

Bronner et al.[11] have nicely summarised the history of the presentation, classification, as well as investigations into IIM over time. IIM was recognised as a clinical entity as early as the late 1800s. However, as noted by this study, it was not until the 1950s that PM was recognised as a stand-alone diagnosis.[11] At that point, Walton[12] noted that PM can occur without skin involvement and that inflammatory infiltrates may not always be present on muscle biopsy histopathology. He also noted that some subgroups of PM have features of collagen disease, or an association with malignancies. In addition, Walton characterised DM with predominant muscle and minimal skin findings, and defined a separate subgroup of collagen vascular disease with some muscle features.

The features of PM were further characterised by Walton and Adams[13] and included symptoms of limb-girdle muscular dystrophies, weakness, pain, arthralgias, and fevers. They also noted an association of PM with connective tissue diseases (CTD) such as SLE, SSc, and RA. These clinical observations of IIM were further clarified and formalised by B and P in 1975.[1]

As time went on, the important findings of muscle biopsy histology were included in the classification criteria. For example, in 1984 Arahata and Engel[11,14] looked at the role of T cells in the pathophysiology of IIM. In 1991, Dalakas[15] suggested diagnostic criteria for IIM based on similar principles of B and P which included muscle biopsy histopathology, as well as addressing the diagnosis of sporadic inclusion body myositis (IBM). However, necrotising autoimmune myopathy (NAM) was not identified as a unique subgroup.

MSA were taken into account in later criteria. For example, Targoff et al.,[16] in 1997, employed the original B and P criteria and classifications, but added the criterion of myositis-related autoantibodies. This was further expanded upon by Troyanov et al.[2] in 2005, with the addition of the subgroup of OM to their classification criteria. However, this classification does not include IBM or NAM.

In 2003, muscle biopsy findings and autoantibodies were both taken into account as part of a proposed classification scheme based on muscle biopsy findings[4,17] Under this classification scheme, the IIMs were divided into DM, PM, sporadic IBM, and nonspecific myositis. In addition, NAM was recognised as a distinct form of autoimmune muscle disease. However, the concept of OM as a stand-alone entity was not directly addressed.

## DEFINITION OF OVERLAP MYOSITIS

As previously mentioned, the B and P criteria do not take into account autoantibodies or clear overlap syndrome (OS) symptoms, which would

more clearly define OM as a stand-alone entity. In an attempt to overcome these deficiencies, Troyanov et al.[2] developed two new classification systems of IIM which focus on overlap disease manifestations. The first classification scheme, named 'the modified B and P classification', added to the original B and P criteria and divided IIM into pure PM, pure DM, OM with at least one clear overlap clinical feature, and CAM with clear paraneoplastic features. The overlap features include polyarthritis, Raynaud's phenomenon, features of SSc such as sclerodactyly, calcinosis, gastrointestinal (GI) abnormalities, ILD, and features of SLE, amongst others.[2]

Their second classification scheme adds, along with the previously mentioned features, autoantibodies associated with OM. These autoantibodies can be subdivided into MSA and MAA categories. Under this scheme, OM would be defined as myositis with at least one clinicaloverlap feature and/or a myositis overlap antibody. These antibodies include anti-synthetase autoantibodies (ASS) as well as SSc-associated autoantibodies, amongst others.[2] However, not all patients with these autoantibodies may actually go on to develop myositis. Alternative labelling has been proposed, including nomenclature such as 'CTM-overlap' and/or ILD autoantibodies.[4]

It is also important to note that IIMs are a subtype of CTD in general. The term mixed CTD (MCTD) is an umbrella term, which includes PM, SSc, RA, and SLE, in association with the presence of a high autoantibody titre to U1 ribonucleoprotein (RNP). It was first described as a distinct entity by Sharp et al.[18] in 1972.[19] While classification criteria for each exist, it is widely recognised that some patients have features of more than one CTD and do not clearly fit into one category. For example, undifferentiated connective tissue disease is considered a unique clinical entity and is characterised by clinical symptoms including but not limited to Raynaud's phenomenon, serositis, fever, arthritis, vasculitis, lung involvement, and myositis.[20] It is thought that an OS occurs when two or more diagnoses of CTD occur in the same patient.[5,11] It has been recognised, however, that in some cases, MSA or MAA may be identified, which would again point towards the idea that the OS are in fact distinct clinical entities.[11]

Bronner et al.[11] summarised two approaches in categorising OS. One approach is the detection of a particular antibody in addition to expected clinical findings; for example, the anti-synthetase syndrome.[12] The second classification encompasses a constellation of clinical findings in the absence of an antibody; for example, RA and SLE overlap, which is known as rhupus syndrome.[11]

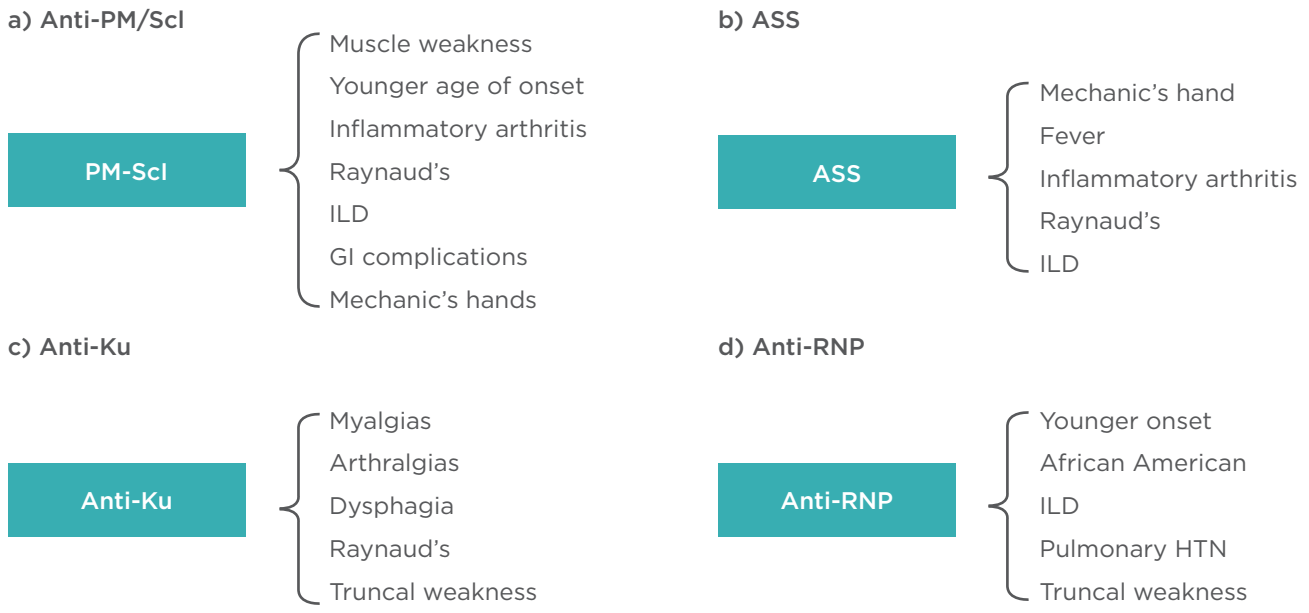


**Figure 1: Autoantibodies associated with overlap myositis/overlap syndrome and associated clinical characteristics.**

PM: polymyositis; ASS: anti-synthetase syndrome; RNP: ribonucleoprotein; ILD: interstitial lung disease; HTN: hypertension; GI: gastrointestinal.

In other studies, the definition of OS has not required the presence of an antibody, but rather clinical features of two different CTD. Moreover, OS has not only referred to a subtype of IIM, but rather a subtype of SSc as well. For instance, Pakozdi et al.[8] reviewed a cohort of patients with SSc. In this study, patients who fulfilled the American College of Rheumatology (ACR) criteria for SSc simultaneously with other CTD features were classified as having an OS. Troyanov et al.[2] noted that SSc is the most common CTD associated with IIM. In fact, Dalakas et al.[15] stated that only SSc and MCTD may truly overlap with DM, not PM.

However, OS/OM should be distinguished from MCTD. Patients with MCTD have features of three different disorders: SLE, SSc, and myositis. MCTD diagnosis also requires the presence of antibodies against a component of the spliceosome complex, the U1 RNP.[14-16] MCTD does not always have IIM as a feature. It has been suggested that up to 72% of patients with MCTD may exhibit a subclinical increase in muscle enzyme levels; however, only 2–3% of these patients present with myositis at first examination. Over half of these patients (51%) may eventually develop subclinical myositis.[17] Clinical presentation is often mild, and most patients respond well to low-dose corticosteroids.[18] However, there is controversy surrounding the concept of MCTD, in that some have considered it as a subset of SLE, and it has also been proposed that eventually MCTD patients will evolve into a definite CTD.[19]

## SUBTYPES OF OVERLAP MYOSITIS ACCORDING TO AUTOANTIBODIES

There are several autoantibodies that have been linked with OM/OS (Figure 1), which may be associated with typical clinical manifestations.

### Anti-Polymyositis/Scl Antibodies

Anti-PM/Scl antibodies are found in DM, PM, SSc, and OM/OS. The PM/Scl complex, also known as the human exosome complex, belongs to a class of antinucleolar antibodies, and is made up of 16 proteins.[9] The major proteins of this complex are named PM/Scl-100 and PM/Scl-75, for their apparent molecular weights.[9] Nakken et al.[20] defined the anti-PM/Scl antibody after describing a group of patients with IIM, in which half of them had features of scleroderma. Anti-PM/Scl antibodies have been found in up to 55% of patients with PM/DM who also presented with features of SLE and Sjögren's syndrome (SS),[9,21] 2–12% of patients with SSc alone,[9,22-24] and 21–24% of patients with PM/SSc overlap.[7,9,25] In the cohort studied by Pakozdi et al.[8] a group of patients with SSc/PM overlap were analysed and it was found that they were positive for anti-PM/Scl antibody in almost a third of cases (33.1%); however, in 17% of cases, this antibody was seen with another CTD or OS.

This antibody is often found in cases of OM or OS. Its main features are muscle weakness, younger age of onset of disease, inflammatory arthritis, Raynaud's phenomenon, ILD, and possible GI dysfunction, although the degree and severity of ILD and GI complications varies among studies. Mechanic's hands (cracking and hyperkeratosis of the radial aspects of the digits), nail-fold capillary changes, puffy fingers, and calcinosis have also been noted.[4]

Subclinical muscle weakness is a common feature in patients with PM/SSc OM. However, this antibody has also been found in individuals with SSc with no muscle involvement at all.[20] Patients tend to be younger at disease onset than typical SSc patients, with milder skin involvement as well as inflammatory arthritis.[4,7,9,26] Raynaud's phenomenon is common, but digital ulceration is rare. In the study by Guillen-Del Castillo et al.,[6] Raynaud's phenomenon and digital ulcerations were found to be less frequent in patients with SSc and ILD who were positive for the anti-PM/Scl antibody when compared with patients with SSc and ILD who were Scl-70 antibody positive; in addition, anti-PM/Scl patients had less GI dysfunction,[6] but there was no difference in the prevalence of calcinosis or inflammatory arthritis. However, myositis was more frequently seen in the patients who were positive for anti-PM/Scl antibodies. Cardiac involvement was similar in both groups. A German registry noted the frequency of PM/Scl antibodies to be 4.9% in their cohort of SSc patients; in these patients, there was a correlation with creatine kinase (CK) elevation, however there was less oesophageal involvement.[27]

A cohort of 40 SSc patients with myopathy were observed in a study by Ranque et al.[28] These patients had muscle involvement, with CK of >5-times the upper limit. Each patient was matched by two control SSc patients for skin involvement, sex, age at SSc onset, and disease duration, without myopathy. The presence of

anti-PM/Scl antibody was significantly associated with myopathy.

ILD is also seen, but tends to be milder than that seen in other CTD or in ASS, and non-specific interstitial pneumoniae may predominate, with higher baseline forced vital capacity values as well as greater rates of improvement during the course of disease.[4] In patients with SSc and anti-PM/Scl antibodies, the prevalence of ILD has been quoted to be between 30–78%.[6] Vandergheynst et al.[29] retrospectively reviewed a cohort of 14 patients with anti-PM/Scl antibodies: 5 had SSc/DM OS, 4 had DM, 1 had PM, 3 had SSc, and 1 had SS. Asnoted in prior studies, the three main features identified in these patients were Raynaud's phenomenon, ILD, and inflammatory arthritis. Similarly, Oddis et al.[25] screened serum samples from 617 patients with various CTD for anti-PM/Scl antibody. Twenty-three patients had these antibodies present; of these, 16 had pure IIM or OM, 6 had SSc alone, and 1 had an overlap of SSc and RA. Overall, it was suggested that this antibody is associated with a subset of patients with CTD, in addition to SSc or myositis features, that present with inflammatory myopathy, arthritis, and limited cutaneous involvement. Troyanov et al.[2] also noted that patients with anti-PM/Scl antibodies had features of inflammatory arthritis, Raynaud's phenomenon, DM rashes, and mechanic's hands, as well as features of SSc.

This phenotype of features of SSc with IIM has been characterised by others; Torok et al.[30] described an entity known as scleromyositis, thought to be a SSc/PM OS with features of Raynaud's phenomenon, myositis, scleroderma, ILD, arthritis, calcinosis, mechanic's hands, and the presence of anti-PM/Scl antibodies. These findings were also noted by Selva-O'Callaghan et al.[31]

Regarding subtypes of anti-PM/Scl antibodies, a study by D'Aoust et al.[9] focussed on the PM-1α antibody, a major epitope of the PM/Scl complex, in patients with SSc. As previous studies have also noted, patients with this antibody were more likely to be younger at the onset of Raynaud's phenomenon, have skeletal muscle weakness, calcinosis, as well as inflammatory arthritis. As in prior studies, ILD and GI involvement was less frequent. Koschik et al.[7] found that the presence of the anti-PM-Scl antibody was associated with OS; namely, SSc associated with features of both PM/DM and SLE, as well as RA. Skeletal myopathy was higher in patients with the presence of anti-PM/Scl antibodies compared to those without. Interestingly, GI involvement was less common in the anti-PM/Scl positive group, and pulmonary fibrosis was more commonly found in patients positive for anti-PM/Scl; however, when detected, the fibrosis was less severe, and pulmonary arterial hypertension (PAH) was also less common. Calcinosis was more common in anti-PM/Scl antibody positive patients, but was not found as frequently in the OS group with anti-PM/Scl antibodies as in the DM group.

Other subtypes of the anti-PM/Scl antibody have also been studied. Hanke et al.[23] looked at the clinical manifestations of patients positive for anti-PM/Scl-75c and anti-PM/Scl-100 autoantibodies in patients with SSc. Muscle disease, pulmonary fibrosis, and digital ulceration were associated with both subtypes. Interestingly, the anti-PM/Scl-75 antibody was found in younger patients with higher activity levels of disease, less GI involvement, but increased joint contractures, and were also found to exist in a subset of patients positive for anti-PM/Scl-75 autoantibodies.[32] In addition, the anti-PM/Scl antibodies were more often seen in patients with diffuse SSc, as opposed to those with PM/SSc overlap; prior studies have shown a higher association in overlap patients.[33,34]

Compared to previous studies, which have looked at the implication of the anti-PM/Scl antibody in SSc, Marie et al.[35] analysed a series of patients with DM/PM based on the B and P criteria, as opposed to OM or OS, who were positive for anti-PM/Scl. None of these patients had evidence of another CTD. The presence of the anti-PM/Scl antibody had a stronger association with lung and oesophageal involvement, which was sometimes severe. Patients with the anti-PM/Scl antibody also presented with ASS symptoms, including mechanic's hands, Raynaud's phenomenon, arthritis, and ILD. The authors have suggested that the presence of mechanic's hands may be a unique distinguishing feature of anti-PM/Scl-positive PM/DM.

## Anti-Synthetase Antibodies and the Anti-Synthetase Syndrome

There are eight autoantibodies that are associated with ASS (Table 1), which target the amino-acyl tRNA synthetase enzymes. ASS has classical clinical manifestations that include myositis, mechanic's hands, fever, non-erosive inflammatory arthritis,

Raynaud's phenomenon, and ILD.[4] However, heterogeneity in the presentation of ASS has been observed. This was demonstrated in a large series of Japanese patients positive for ASS antibodies, where there were variations regarding distribution and onset of manifestations of ASS.[36] Regarding typical systems of ASS, Bhansing et al.[10] noted features such as mechanic's hands, Raynaud's phenomenon, ILD, arthritis, and myositis in a subgroup of patients with SSc-PM OS who were positive for anti-Jo-1 antibodies. As previously mentioned, Troyanov et al's.[2] second classification system included ASS antibodies. They found that anti-Jo-1 was the most commonly seen antibody in OM, with clear features of ASS. Almost half of these patients presented with high initial CK levels (>9000 U/L). Other ASS autoantibodies were also identified, including anti-PL7 and anti-PL12; these patient groups presented with severe ILD. A single patient tested positive for anti-KS autoantibodies, and their presentation was unique for features of digital ischaemia as well as deep vein thrombosis. Interestingly, ASS autoantibodies were markers for a chronic myositis course.

The anti-Jo-1 autoantibody was noted to be the most frequently seen of all the ASS in the study by Love et al.[38] in 1991 in a population of patients with IIM. This study found that in the IIM patients who were studied, autoantibodies were present in all clinical groups; anti-nuclear antibodies (ANA) were significantly more frequently found in patients with another CTD than with PM, IBM, or CAM. After ANA, ASS were most commonly seen, with anti-Jo-1 being the most frequent. They also found that the majority of patients with anti-Jo-1 antibodies had PM. It is interesting to note that some features of the ASS, for example ILD and Raynaud's phenomenon, are also features of SSc. Troyanov et al.[2] raised the question as to whether the extra-muscular manifestations of ASS are actually more in keeping with SSc.

Regarding the issue of muscle biopsy, a recent international workshop on the pathological diagnosis of IIM noted a discussion of typical muscle biopsy findings in ASS. Findings on muscle biopsy include inflammatory perimysial fragmentation, sarcolemmal membrane attack complex deposit staining on fibres next to the perimysium, as well as fine filaments in myonuclei present on ultrastructural examination.[39]

## Anti-Ku

When found in SSc patients, anti-Ku autoantibodies are often associated with SSc OS, namely features of SSc with muscular involvement.[10,27] Cavazzana et al.[40] found that patients with anti-Ku antibodies presented with undifferentiated CTD or OS, including PM and SSc.

In patients with PM/SSc OS, the prevalence of anti-Ku antibodies in sera has been quoted to range between 2.3–55%.[27] A retrospective review by Pakozdi et al.[8] reported on a cohort of patients with SSc/myositis OS, and found that anti-Ku antibodies were uncommon. This autoantibody was detected in 2.3% of SSc/IIM and 1% of SSc/RA. Similar to their findings with the anti-PM/Scl autoantibody, Troyanov et al.[2] found that, in their cohort, patients with anti-Ku antibodies presented with features of RA and SLE. In terms of cutaneous involvement, Kaji et al.[41] studied a cohort of patients with SSc and myositis features; they found that the presence of the anti-Ku autoantibody was less associated with DM rashes than anti-PM/Scl.

**Table 1: Antisynthetase autoantibodies and associated antigens.[37]**

| Antisynthetase Autoantibody | Antigen |
|---|---|
| Anti-Jo-1 | Histidyl t-RNA synthetase |
| Anti-PL-7 | Threonyl t-RNA synthetase |
| Anti-PL-12 | Alanyl t-RNA synthetase |
| Anti-EJ | Glycyl t-RNA synthetase |
| Anti-OJ | Isoleucyl t-RNA synthetase |
| Anti-KS | Asparaginyl t-RNA synthetase |
| Anti-Zo | Phenylalanyl t-RNA synthetase |
| Anti-Ha | Tyrosyl t-RNA synthetase |

Rigolet et al.[42] studied a cohort of patients who tested positive for anti-Ku antibodies. Thirty-seven percent of patients had IIM, the majority of these patients as part of an OS, with features of SSc, SS, and SLE. Patients with IIM OS had clinical features including myalgia, proximal muscle weakness, dysphagia, and increased CK. ILD was also noted, which in the majority of cases was corticosteroid resistant, as well as Raynaud's phenomenon and arthalgias.

An interesting phenotype of IIM, known as camptocormia, characterised by truncal weakness, has been described in association with anti-Ku antibodies. Zenone et al.[43] reported such a case of myositis with Raynaud's phenomenon, muscle necrosis, and sclerodactyly, leading to a PM/Scl OS diagnosis. Camptocormia has also been reported in other patients with IIM.[44,45]

## Anti-Ribonucleoprotein

Anti-RNP antibodies are antibodies against the RNP complex, and include anti-U1-RNP and anti-U3-RNP. Antibodies to U3-RNP are most often seen in diffuse cutaneous SSc myositis OS.[41] Seen more frequently in African-Americans, patients may be younger at disease onset, and have consistent features of myositis, ILD, renal, and cardiac involvement. PAH is associated in particular with diffuse cutaneous involvement and the presence of anti-U3-RNP.[10] These findings were corroborated by Aggarwal et al.,[26] who also noted a poor prognosis in patients with SSc and anti-U3-RNP antibodies. In their cohort, almost all SSc patients positive for anti-U3-RNP antibodies had SSc alone (925), and 8% had an OS. The percentage of patients with OS was similar to that of patients negative for the anti-U3-RNP antibody. This antibody was not seen more frequently in patients with diffuse versus limited skin findings of cutaneous SSc; however, in the OS population, patients positive for anti-U3-RNP presented with predominantly diffuse SSc. Eight of the nine anti-U3-RNP positive patients with OS had myositis, and the remaining one had SLE. Patients with OS and IIM presented less frequently with CK elevation and had less inflammation on muscle biopsy.

Pakozdi et al.,[8] in their study of patients with SSc overlap syndromes, the presence of anti-U1-RNP was more frequently found in patients with SSc/SLE. In the study by Troyanov et al.,[2] anti-U1-RNP antibody was associated with a monophasic course of IIM. In their cohort of patients with OM, SSc-associated autoantibodies were present in 34% of the OM patients, with anti-U1-RNP being the most common antibody, being present in 13% of patients.

## CONCLUSION

IIM may be associated with OM/OS, and include features of other CTD such as SSc, SLE, RA, or SS, apart from myositis seen in MCTD. Certain autoantibodies may be associated with phenotypical clinical presentations.

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# UPCOMING EVENTS

## German Society for Rheumatology (GSR) 44th Congress 2016

*31st August–3rd September 2016*

*Frankfurt Am Main, Germany*

With this year seeing a change of location to accommodate the growing number of attendees, the 44th Congress of the German Society for Rheumatology will exhibit a combination of the latest research, particularly with regard to rare rheumatological diseases, and the traditional patient event, promoting the collaboration of physician and researcher, young and old alike. Abstract topics include experimental rheumatology, epidemiology, and connective tissue diseases, amongst many others.

## 16th Mediterranean Congress of Rheumatology (MCR) 2016

*1st–4th September 2016*

*Sarajevo, Bosnia and Herzegovina*

Aimed at developing international working relationships between rheumatologists, this event will see different approaches and perspectives collide in an effort to advance the field of rheumatology. Presentations and discussion drawn from a varied pool of interests and backgrounds will ensure a wide spectrum of topics for debate and consideration; this multidisciplinary theme is beautifully reflected in the choice of a multicultural host location: the vibrant and historic city of Sarajevo.

## 15th International Congress on Antiphospholipid Antibodies (aPL) 2016

*21st–24th September 2016*

*Istanbul, Turkey*

One of the more specifically themed congresses to be held in rheumatology this year, the International Congress on Antiphospholipid Antibodies will present a range of evidence-based research from across the world concerning antiphospholipid syndrome and its role in the pathogenesis of other diseases. Highlights include a full day of state-of-the-art lectures on Lupus Bosphorus, and the exploration of genetics, immunotherapy, diagnosis and management, and paediatric antiphospholipid syndrome.

## 13th International Cartilage Repair Society (ICRS) World Congress

*23th–27th September 2016*

*Sorrento, Italy*

This congress will reflect the dynamic nature of cartilage injury and repair and is an opportunity eagerly taken by the International Cartilage Repair Society to prove itself as a pre-eminent organisation in the field. The programme will feature emerging trends and controversies such as the use of stem cells, growth factors, and gene therapy, while aiming to bring scientists and clinicians together to share and discuss ideas.

## British Society for Rheumatology (BSR) Autumn Conference

*13th–14th October 2016*

*Bath, UK*

The 2-day conference will host consultants and next-generation rheumatologists sharing their insights on best clinical practice through case-based discussions focussing on four main areas. These areas will be Raynaud's disease, spondyloarthropathies, vasculitis, and infection and arthritis. There will also be a keynote talk delivered by Prof Peter Taylor who holds the Norman Collisson chair of musculoskeletal sciences at the University of Oxford, Oxford, UK.

## 4th World Congress on Controversies, Debates and Consensus in Bone, Muscle, and Joint Diseases (BMJD)

*20th–22nd October 2016*

*Barcelona, Spain*

The fourth congress will continue its facilitation of debates by tackling the therapeutic and clinical dilemmas currently facing experts treating bone, muscle, and joint diseases. The various debates taking place will draw on contentious issues such as the contemporary role of corticosteroids in rheumatoid arthritis. They will also include the best approaches for treating musculoskeletal pain and whether pain relief should be considered beneficial for patients with osteoarthritis.

## 18th Annual Congress of the Croatian Rheumatology Society (HRD)

*20th–23rd October 2016*

*Šibenik, Croatia*

This event will continue in its annual tradition of aspiring to achieve the same basic goal: improving care for rheumatic patients. In doing so, it will provide a series of scientific and technical lectures delivered by clinicians and researchers reporting on their own experiences and research findings. A platform will also be provided for early-career rheumatologists to present their own original research and achievements, with a workshop on the basics of diagnostic ultrasound applications also offered.

## European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology

*14th–17th June 2017*

*Madrid, Spain*

Since its inception in 2000, the annual EULAR congress has grown to become one of the leading events in the field of rheumatology. Each year it has provided an innovative platform for the exchange of novel and impactful clinical and scientific research for the treatment of rheumatic and musculoskeletal diseases (RMDs). EULAR 2017 will prove to be a continuation of this trend, serving the ever-increasing interest in RMDs across both Europe, and around the world. It will do so by providing a scientific programme that is filled with a wide range of topics, including clinical innovations and the latest advances made in both translational and basic science.

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